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THE VALUE OF PROTEIN AND ITS CHEMICAL COMPONENTS (AMINO ACIDS) IN SURGICAL REPAIR*

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THE role of protein nutrition in repair may be discussed under three headings: 1) wound healing; 2) maintenance of tissue integrity; and 3) convalescence. I shall discuss the first two topics briefly, take up the subjects of the loss of nitrogen in disease; the consequences of protein loss to the body; and the inadequacy of natural food to replenish this loss. Then I shall discuss our studies on convalescence, presenting our work in five categories. Finally, I shall discuss the role of hydrolysates and amino acid mixtures in clinical nutrition.

Wound Healing: The older work by Clark[1] and Howes[2] on wound healing was brought closer to the clinic by the series of studies by

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The work described in this paper was initiated under a grant from Mead Johnson and Company and is being continued under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and New York University. It was the product of the work of a team consisting of Drs. Arthur Mullin Wright, J. H. Mulholland (now Lt. Col., M.C., A.U.S.), Irving Barcham, George R. Gerst, and many members of the Surgical Staff of New York University College of Medicine and the New York University Surgical Division of Bellevue Hospital, as well as of Lilly Schmidt and her staff of chemists and Mary Coughlin and her nursing staff.

Ravdin and his associates[3, 4, 5, 6] on the relation between wound dehiscence and hypoproteinemia in dogs. These authors attributed wound disruption to two factors, edema and incapacity to form fibroblasts as a result of the lack of building material. Whipple[7] in 1940 in his presidential address before the American Surgical Society laid special emphasis on the relation between the lag period of wound healing and protein nutrition, and it is now the consensus of well-informed surgical opinion that protein deficiency plays an important role in wound dehiscence.

Tissue Integrity: The role of protein nutrition in the maintenance of tissue integrity was suggested by our observations on non-neurologic cases of bed sores.[8] In this study a close association was found between the occurrence of bed sores and the plasma protein level, all patients with bed sores having levels mostly below 5.5 grams per cent and never over 6.35, and a negative nitrogen balance. When the nitrogen balance was reversed from negative to positive, the bed sores healed promptly. This finding led to the formulation of the hypothesis that bed sores are pressure sores occurring in tissues which, as a result of being devitalized by protein deficiency, undergo pressure necrosis more readily than normal tissues. It must be mentioned that bed sores do not occur in cases of nephrosis, even with a plasma protein level of 3.5 grams per cent. It is possible that tissue edema, by more equally distributing the pressure, prevents this.

Production of Protein Deficiency: How is protein deficiency produced? In experimental animals it can be produced by a protein-poor diet, by plasmaphoresis, or by a combination of both.[9, 10] Clinically, similar mechanisms are operative and in addition, a third one, namely, increased metabolic loss of nitrogen as a result of injury or disease. The combination of decreased intake and increased output can deplete the protein stores in a few days.

Decreased intake may be caused by poor appetite, and it may here be said that appetite, while a good guide to nutrition in health, is a poor guide in disease. The occurrence of actual nausea, vomiting and pain also decreases intake. Then there may be poor absorption from the gastrointestinal tract as a result of diarrhea, of hyperperistalsis or of a diseased mucosa. Poor intake may also be due to neglect on the part of the attendants; that is, a physician may not prescribe an adequate diet or fail to watch the patient's nutritive status. Many surgeons have de-

TABLE I

NITROGEN CONTENT OF HOSPITAL WARD DIET

	Total nitrogen, gram
Wednesday	6.245
Thursday	14.827
Friday	8.189
Saturday	5.211
Sunday	8.6846
Monday	10.338
Tuesday	12.484
Total Nitrogen for week	65.94
Average Nitrogen per day	9.42

veloped an over-dependence on blood transfusions, expecting an occasional blood transfusion to supply a patient's caloric and nitrogen requirements for a week. Lastly, the hospital diet may be sub-standard. Charity hospitals are the greatest offenders in this respect. Table I shows the nitrogen contents of the basic diet of a charity hospital for a period of a week. This basic diet was based on Sherman's recommendation[11] for healthy individuals but has been adopted indiscriminately generally by hospitals as an adequate basic diet also for hospital patients. It will be seen that on most days the intake falls below the prescribed minimum and that the average is in the neighborhood of 9.5 grams of nitrogen per day.

Increased Metabolic Loss: The average nitrogen loss in the urine of a healthy adult is about 13.5 grams nitrogen per day.[12] This amount goes down in starvation. During disease it may go up to two or sometimes three times this figure, as found by Cuthbertson[13] and confirmed by a number of other workers, prominently among them Browne,[14] Albright[15] and Howard.[16] This increased loss has been attributed to a number of factors, among them injury and autolysis of tissues and to an endocrine factor supposed to be elaborated by the cortex of the adrenal gland. This increased loss has sometimes been called "toxic loss of nitrogen" or "catabolic loss." Whether the nitrogen lost is all replaceable has been a moot point; some workers think this can be accomplished, while others do not. As a result of recent work, it seems that the con-

TABLE II

CASES OF BURNS RE-ARRANGED ACCORDING TO PERCENTAGE OF BODY SURFACE INVOLVED

Name	*Body Surface Burned %*	*Age of Burns Days*	*Nitrogen Loss Grams Per diem*
F.W.(1)	8	40	4.07
F.W.(2)	10	8	1.58
J.Mc.	15	21	2.98
J.W.	15	23	7.65
J.S.	15	4	1.79
A.B.	20	2	1.5
J.Mc(1)	21	15	3.56
J.Mc(2)	30	6	5.15
M.W.	40	94	6.45+
A.F.	50	4	9.07+

ditions in which this loss has been thought irreplaceable have been narrowed down. The question still remains: In what disease states and under what conditions is this metabolic loss replaceable?

Loss in Exudates: Another avenue of loss of nitrogen is in exudates and other body discharges.[17] This is comparable to plasmaphoresis in experimental animals. Table II shows the amount of nitrogen lost per twenty-four hours in cases of burns. It will be seen that A.F., with 50 per cent surface involved in burns, lost at least 9 grams of nitrogen per day (some leakage having occurred into the beddings). This represents about 55 grams of protein or about one-third of the amount present in the blood. Were it all to come acutely from the blood, this amount of loss alone would have led almost to the development of shock.

Table III shows the amount of nitrogen lost in the exudates of different surgical conditions. S. S. had an avulsion of the perineum and back, covering about 15 per cent of body surface. Three months after his injury he was still exuding 6.37 grams of nitrogen in twenty-four hours, which is equivalent to 664 cc. of plasma. R. W. was a case of radical mastectomy who lost 4.26 grams of nitrogen in the first twenty-four hours, dwindling down to 1.2 grams in three days. A. G., who had an abdomino-perineal resection for carcinoma of the rectum, lost 6.22 grams of nitrogen in the first twenty-four hours. This loss had decreased

TABLE III

NITROGEN LOSS IN DIFFERENT EXUDATIVE SURGICAL CONDITIONS

Name	*Diagnosis*	*Date of Injury or Operation*	*Date Collect.*	*Total N Exuded 24 hrs., gm.*	*Equiv. in Proteins gm.*	*Equiv. in Plasma cc.*
S.S.	Avulsion Perineum and Back	7/7	10/23	6.37	39.81	664
R.W.	Radical Mastectomy	10/25	10/26 10/30	4.26 1.2	26.65 7.50	445 125
A.G.	Abd-Perineal Resection (Cancer-rect)	8/13	8/14 8/16	6.22 2.07	38.87 12.97	644 216
O.Mc.	Abd-Perineal Resection (Infected Cancer-rect)	8/9	8/18 8/21	6.97 3.47	42.46 21.69	707 723
F.C.	Lung Abscess Pyothorax		4/24	9.57—	59.8—	996
A.C.	Empyema			9.37	58.56	976
H.L.	Liver Abscess (5 cm. diam.)	12/26	12/28	1.98	12.63	210

to 2.07 in twenty-four hours. Both of these cases suggest an effort on the part of the body to seal off exuding surfaces. O. Mc. was a case of abdomino-perineal resection which was infected. The loss in the pus nine days after operation was 6.9 grams but within three days after drainage was instituted, it had decreased to 3.47 grams. F. C. and A. C. were, respectively, cases of lung abscess with pyothorax and of empyema. They lost respectively 9.57+ and 9.37+ grams, equivalent to almost 1,000 cc. of plasma or about one-third of the amount of circulating protein in the blood. This magnitude of loss may in part account for the emaciation and high mortality observed in this type of case. Our experience with the burn cases makes us hopeful that chest cases of this type may respond favorably to full nitrogen replacement.

Consequence of Large Protein Loss: Some of the consequences of large protein loss have been implied in the remarks on wound healing and on the maintenance of tissue integrity and need not be repeated. When the loss is large and acute, such as that which occurs in burns, the osmotic component of the blood can be so depleted as to cause shock.

TABLE IV

NITROGEN VALUES OF VARIOUS HOSPITAL DIETS

	Protein gm.	*Total N gm.*	*N in gm. kgm.*
Basic	70	11.2	.186
High Protein (1)	120	19.2	.32
High Protein (2)	130	20.8	.346
Tolerance[1]	192	30.7	.512

[1] By tolerance is meant the amount taken to the point of satiety.

In the cases of more chronic losses, although the hypovolemia may be better tolerated, the patient must be expected to be a poorer risk as a result of the hypovolemia.

The blood plasma level does not always indicate a diminished total blood protein but it may be safely stated that a blood plasma protein below 6.0 grams per cent is indicative of protein deficiency. Five grams per cent is usually called the critical level of clinical edema.[10]

Digestive disturbances in the form of delayed emptying time and even of vomiting and diarrhea[6] may be symptoms. This would cause a vicious circle in further decreasing the intake.

There is also evidence to show that antibody formation is hindered.[18]

A set of mental symptoms in the form of confusion, apathy and incontinence of urine and feces has also been noted to be associated with protein deficiency.

Lastly, convalescence appears to be retarded by protein losses which are not replaced, resulting in long continued weakness and incapacitation. This we shall discuss later.

Inadequacy of Natural Food: Assuming that the replenishment of the nitrogen lost is both desirable and feasible, the question arises as to the adequacy of natural food for this purpose. Table IV shows the range of nitrogen values of the standard hospital diets. It will be seen that the ceiling of nitrogen intake is set by the "high protein diet" which contains approximately 20.8 grams of nitrogen. Considering that it takes more than 1 gram of nitrogen in the intake to replace 1 gram of nitrogen lost from the body, it is readily understandable how inadequate this

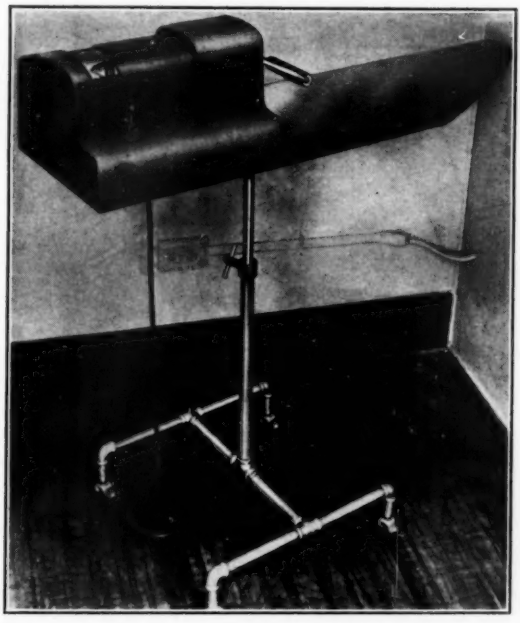

Fig. 1. Improved bedside ergograph with mechanism enclosed.

"high protein diet" is to a person who is losing 20 grams of nitrogen in the urine and 6 to 9 grams in an exudate. The gap between the low ceiling of nitrogen intake possible with natural food and the large losses occurring in trauma and disease can be filled to a fair degree of adequacy by protein hydrolysates such as amigen.

Convalescence: I shall now take up our studies on convalescence in five clinical categories; namely, burns, gastrectomy, herniotomy, cholecystectomy, and finally peptic ulcer; and incidentally show the value of hydrolysates. Except for the cases of burns, the complete nitrogen balance was followed in all of the cases for from a week to twelve days. Also determined were the body weight and in many cases, the endurance as tested by the bedside ergograph.

The original model of this ergograph was described in a previous communication.[19] The improved model is shown in Figure 1. The E.T. or ergograph time is the number of seconds a patient is able to lift a known weight until fatigue sets in. Objection to the use of the ergograph has been advanced on the basis that both motivation and the

TABLE V

NITROGEN INTAKE IN PATIENTS WITH BURNS FED WITH PROTEIN HYDROLYSATES

Patient	*Original Body Wgt. Kgm.*	*Area Burned %*	*Total Daily N Intake gm.*	*N in gm. Wt. Kgm.*	*Equiv. Plasma cc.*	*Remarks*
J.C.	56.8	10	35	0.62	3644	Sufficient
J.McN.	55.45	30	24	0.43	2500	Insufficient
			25.6	0.46	2650	Insufficient
			33.6	0.61	3500	Maintenance
			42.2	0.76	4400	Rapid Gain
M.W.	65.9	50	27.44	0.42	4570	Insufficient
			36	0.55	3750	Maintenance
			49.5	0.75	5160	Slight Gain
			66	1.00	6875	Rapid Gain

learning process, which have been found to affect ergography on normal subjects, may introduce sources of error in tests in convalescence. However, the factor of motivation in severely ill patients may be considered a minor one, since most patients are eager to show as good results as possible. The matter of training may also play but a small part, since these tests were made not more often than once in two or three days. In any event, the results have been striking and consistent, showing a gradual increase when the patient improved and was on positive nitrogen balance, and a decline when the patient declined and was on negative nitrogen balance.

The period of recumbency has also been taken as a criterion of recovery, although it is only a relative one, since the practice of forced early ambulation has itself shortened convalescence, perhaps by stimulating appetite and promoting an earlier establishment of positive nitrogen balance. The patients reported in these five groups were all from a surgical service that does not practice early ambulation, so that the factor of more prolonged bedrest is common to all.

Burns: I shall first take up three cases of burns as shown in Table V which have been reported elsewhere.[20] It will be seen from the table that there seems to be a fairly close relationship between the area of burned surface and the amount of nitrogen intake necessary to maintain nutrition. Thus, J. C., who had only 10 per cent of his body area burned,

TABLE VI

LOW NITROGEN INTAKE POSTGASTRECTOMY

Name	*N Intake Wt. gm.*	*N Loss Wt. x Day gm.*	*Days Under Study*	*Loss of Wt., Kg.*	*Return of E.T., Days*	*Days in Bed*	*Remarks*
P.B.	.04	.153	8	4.27		23	
F.Mc.	.04	.015	12	6.59	Not 12th	17	
J.S.	.04	.207	8	3.89		17	
D.F.	.052	.165	11	.9		35	Evisceration
N.G.	.06	—	12	7.8		24	
A.D.	.07	.183	10	4.78		19	
G.W.	.08	.089	13	5.26		17	
R.B.	.095	.159	8	.48		21	
F.W.	.095	.065	12	4.45		21	
M.K.	.11	.237	9	6.19	Not 12th	13	Amigen-prepared
W.C.	.18	.088	9	4.05		13	Amigen-prepared
J.B.	.19	.078	10	1.7		37	
A.S.	.27	.015	9	4.37		17	
				Average Days		21.07	

was able to support nutrition on 35 grams of nitrogen in the form of amigen. For J. McN. with 30 per cent of body surface burned, 25.6 grams nitrogen was insufficient, 33.6 maintained nutrition, whereas 42.2 resulted in rapid gain. M. W. with 50 per cent of body surface burned, lost ground on 27.44 grams nitrogen, was maintained on 36 grams, registered slight gain at 49.5, and rapid gain at 66. All these values are much larger than the amount of nitrogen available in even the hospital high protein diet.

Gastrectomy, Cholecystectomy and Herniotomy: The next series were gastrectomy cases. There are thirteen cases on low protein intake in Table VI, the intake ranging from .05 to .27 grams of nitrogen per kilogram body weight. The nitrogen losses/KBW ranged from .015 grams [.19 GM/KBW] in the case of F. Mc. to .237 in the case of M. K. The body weight loss ranged from .48 kilograms in the case of R. B. to 6.59 kilograms in the case of F. Mc. The strength as measured by the

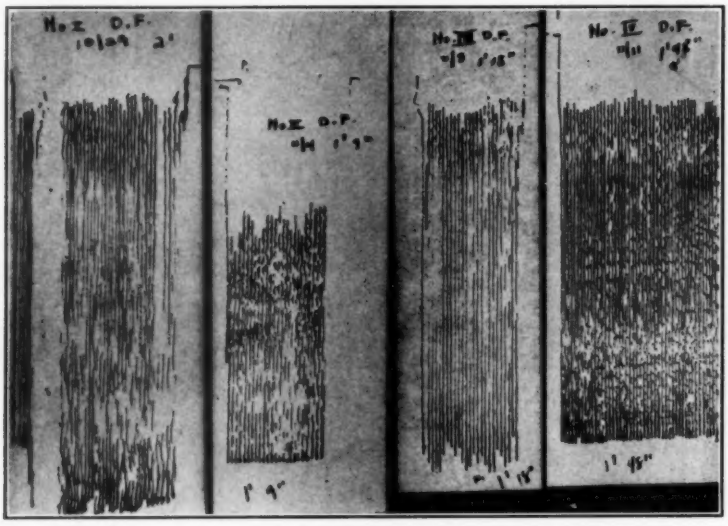

Fig. 2. Ergogram of Patient D.F. (Table VI). Low protein intake postgastrectomy. Initial ergogram: E.T. was 2'. The three subsequent ergograms were respectively 6, 10 and 13 days after operation. Note that on the thirteenth day, E.T. had not returned to the initial reading.

TABLE VII

HIGH NITROGEN INTAKE POSTGASTRECTOMY

Name	*N Intake Wt. gm.*	*N Gain Wt. x Day gm.*	*Days Under Study*	*Wt., Gain kgm.*	*Return of Endurance*	*Days in Bed*
A.V.	.25	.069	7	1.14		22
G.H.	.42	.049	13	2.2		13
V.B.	.434	.169	12	4.71		14
P.R.	.44	.077	8	4.54		8
G.S.	.44	—	8	6.0		8
A.V.	.48	.14	11	4.54	Before 8th	9
F.R.	.482	.217	11	3.95		17
A.H.	.5	—	—	4.0		10
C.N.	.6	.212	12	5.3	Before 8th	10
R.B.	.6	.241	10	4.32	Before 8th	10
E.B.	.61	.303	11	5.85		10
P.F.	.692	.2	12	4.21		14

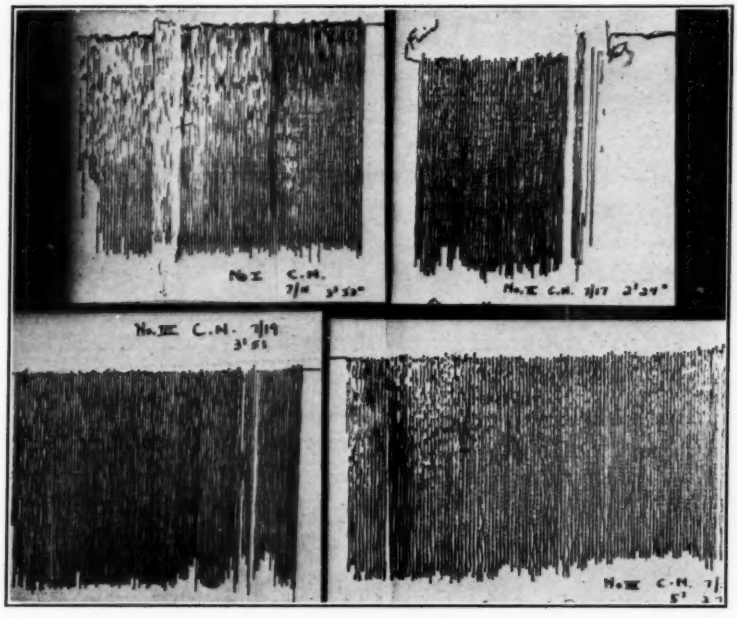

Fig. 3. Ergogram of Patients C.N. (Table VII). High protein intake, gastrectomy case. Panel I is the initial ergogram. Subsequent ergograms, 4, 6 and 12 days after operation. Note that by the sixth day, the E.T. had topped the initial reading.

ergograph had not returned by the twelfth day in any of the patients tested. Figure 2 shows one such an ergogram. The average number of days which the patient stayed in bed was 21.07. M. K. and W. C. were both fed with amigen until they felt strong and gained weight at least a week before they were sent to the operating room. Their ability to get up in thirteen days indicates the importance of the pre-operative period of up-building and the usefulness of hydrolysates in the up-building of malnourished patients.

Table VII summarizes twelve similar cases on high nitrogen intake following gastrectomy, the nitrogen and caloric intake again consisting of amigen and dextri-maltose fed for the first four to six days through the jejunal lumen of a double-lumened tube, the other lumen lying in the stomach for the purpose of keeping the viscus deflated. After withdrawal of the tube, the feeding was given orally. It will be seen that the level of intake was .25 grams of nitrogen/KBW or over. All the patients

were in positive nitrogen balance, gaining from .069 grams of nitrogen per KBW in the case of A.V. to .3 in the case of E.B. The weight gain ranged from 1.14 to 6 kilograms. The endurance returned by the eighth day, and Figure 3 shows the ergogram of C.N. The number of bed days averaged 12.8, an average which was not quite fair since any attempt at a reduction of bed days in patients of this type runs counter to surgical tradition and is usually resisted, eventually resulting in a prolongation of bed rest. The final number of eight to nine days is therefore the more faithful time of bed rest.

Putting these two tables together, one finds that under an intake of .19 GM/KBW the patients were always in negative nitrogen balance and lost weight and that the E.T. declined significantly in all the cases tested. One patient, A.V., with an intake of .25 grams nitrogen per KBW* was in positive balance, whereas another patient, A.S., was in negative balance on .27 grams nitrogen per KBW, denoting that there is an intermediate zone in which some cases will register a negative balance while others, a positive balance. All patients having an intake of .42 grams per KBW and over were in positive nitrogen balance and all gained weight; and all those tested showed an early return of endurance as shown by the early decrease of E.T. Both of these tables were rearranged from tables which appeared in two previous reports.[20, 21]

The third series of cases were cholecystectomy cases which are represented in Table VIII under both low and high intakes. In this series, when the intake was below .224 grams per KBW, there was a negative balance, whereas above .339 grams per KBW, there was always positive nitrogen balance. The weight and ergogram show the same trend as in the gastrectomy cases. This series is still too small, as there is too large a gap between the unit intakes of .224 and .339 grams per KBW.

The last series are seventeen cases of hernioplasty, twelve unilateral and five bilateral. This study was undertaken not because the nitrogen loss after herniotomy is an apparently important factor in convalescence but to test the theory that normal persons subjected to operative trauma undergo a nitrogen loss which cannot be replaced. Most of these patients were in good nutrition, so that except for their structural defects, they may be considered normal persons who had suffered operative trauma.

Table IX summarizes the nitrogen balance studies. Part A embodies the twelve cases of unilateral hernioplasty and Part B, the five of bi-

* In the balance of this paper "KBW" will denote Kilogram Body Weight.

TABLE VIII

NITROGEN INTAKE POST-CHOLECYSTECTOMY

Name	*N Intake Wt., gm.*	*N Gain or Loss Wt. x Day*	*Days Under Study*	*Wt., Gain or Loss (kgm.)*	*Return E.T. (day)*	*Bed Days*
A.C.	.089	—.104	12	—3.9		35
A.J.	.058	—.12	10	—2.8	not on 14th	18
M.R.	.224	—.026	14	—1.36		19
R.V.	.339	.168	10	2.74		10
P.F.	.348	.143	10	2.77		12
E.S.	.382	.082	12	1.2		12
L.M.	.402	.3285	10	3.7	6th	8
A.S.	.43	.049	10	1.17	8th	10
F.S.	.456	.204	12	1.0		12

TABLE IX

UNILATERAL HERNIOPLASTY: Group A

Name	*N Intake gm. per kgm.*	*N Balance per day*	*Number of Days*	*Wt. Change (kgm.)*	*E.T.*
A.S. (1)	.059	—.111	9	—1.02	
(2)	.087	—.086	9	—1.59	
A.B.	.104	—.06	10	—1.37	273-243
O.V.	.131	—.07	10	—1.5	377-260
V.P.	.147	—.011	10	— .45	
J.B.	.182	.011	10	— .37	500-510
H.G.	.258	.002	10	.5	372-390
P.N.	.35	.046	10	0	
W.J.	.363	.045	7	?	
M.S.	.38	.11	10	2.01	
J.F.	.45	.131	10	2.02	
D.F. (1)	.446	.127	10	2.22	
(2)	.454	.147	8		
J.D.	.53	.033	10	1.59	

BILATERAL HERNIOPLASTY: Group B

A.T.	.13	—.152	10	—2.9	
S.J.	.156	— .072	10	—2.27	
B.A.	.335	.066	8	.9	
C.L.	.373	.003	10	.3	
J.F.	.395	.004	10	.31	

lateral. A.S. and D.F. in Part A both had bilateral hernias, one of which was operated upon several days after the other. It will be seen that at the second operation the loss of nitrogen in grams per KBW did not differ radically from the first operation a week or so earlier. It will also be seen that on an intake of .182 grams per KBW, there was a negative nitrogen balance. The ergograph time (E.T.) in this group with the negative nitrogen balance was significantly depressed in one, O.V., and very slightly but not significantly in two; that above .258 grams per KBW there was a consistent positive nitrogen balance with gain in weight.

A comparison of the nitrogen loss or gain per KBW in simultaneous, bilateral hernioplasty with that in unilateral hernioplasty is interesting. Thus, if we match A.T. in Group B, intake .13 grams per KBW, with O.V. in Group A, intake .131 grams per KBW, we see that A.T. lost .152 grams nitrogen per KBW, as compared with the loss of only .07 grams in O.V., and the weight loss of the former was 2.9 kilograms as compared with 1.5 in the latter. S.J. in Group B, with an intake of .156 grams per KBW, if matched with V.P. in Group A, who had an intake of .147 grams per KBW, lost .072 grams nitrogen per KBW, while V.P. lost only .011 grams. The weight loss of S.J. was 2.27 Kgm. as compared with the loss of only .45 Kgm. in V.P. Again, if C.L., with unit intake of .373 grams of nitrogen is matched with W.J. with unit intake of .363 it is seen that C.L. gained only .003 grams of nitrogen per KBW, whereas W.J. gained .045. Lastly, if J.F., Group B, with intake of .395 grams per KBW is matched with M.S. on .38 grams per KBW, it will be seen that the former gained only .004 grams per KBW, whereas the latter gained .11 grams.

These figures suggest that the loss of nitrogen in hernioplasty may not all be attributable to the nitrogen loss due to bedrest and that the extent of operative trauma plays a role. It also shows that the post-operative loss of nitrogen, even in previously normal persons, is correctable, at least in some types of cases. Both Elman[22] and Peters[23] have also found that cases of hernioplasty can be readily put into positive nitrogen equilibrium.

Parenthetically, the hope may be expressed that herniotomy cases in good nutrition, because of the fairly well standardized surgical trauma inflicted, may be used to compare the biological value of different hydrolysates on the human body. Thus, if a hydrolysate X cannot support

N equilibrium at a level of intake of about .182 grams nitrogen per kilogram body weight, it would be inferior to amigen, while one which can do this at a lower level might be considered of superior biological value.

A correlated view of the studies of these four surgical categories; namely, burns, gastrectomy, cholecystectomy and herniotomy, suggests that there may well be a critical level of nitrogen intake peculiar to each category to maintain the patients in nitrogen equilibrium. Only a further study will confirm or refute this possibility.

Peptic Ulcers: The fifth series of cases is of peptic ulcers treated with protein hydrolysates and high caloric diet. The series of twenty-nine cases may be classified as follows:

16	duodenal ulcer
5	duodenal and gastric ulcer
6	gastric ulcer
2	gastro-jejunal ulcer
29	
13	"intractable"
6	with retention (20-100%)
6	with frank hemorrhage

All were treated with from .5 to .6 grams nitrogen per KBW, in the form of amigen, and enough dextri-maltose to make up to 40 C per KBW. This is approximately 5 grams each of amigen and dextri-maltose per KBW. The mixture is suspended in water, divided into eight to nine feedings, and given at two-hourly intervals. Feedings were continued two or three weeks exclusively, depending upon the clinical response and x-ray findings. No antacids or antispasmodics were given, and wherever necessary, amphojel in 4 cc. doses was given twice a day to control diarrhea. A full complement was added to the feeding. The results may be summarized as follows:

Pain and distress stopped in twenty-four to forty-eight hours. Vomiting stopped forty-eight hours after institution of the feedings; rapid roentgenologic healing; positive nitrogen balance, averaging 10 to 16 grams (first ten days); gain in weight, 1 to 8 Kilos in two to three weeks; and rapid gain in strength and morale. However, the treatment does not prevent recurrence on resumption of old dietary habits.

Figures 4 and 5 show the progression of healing in two gastric ulcer cases. One interesting feature in connection with these ulcer cases is the great improvement in endurance as may be seen in the ergogram of patient E.B. in Figure 6.

Figure 4A. Patient C.B. Large crater, lesser curvature.

Fig. 4B. Patient C.B. Almost complete healing in 10 days.

Fig. 5A. Patient R.B. Large ulcer crater, lesser curvature pars media.

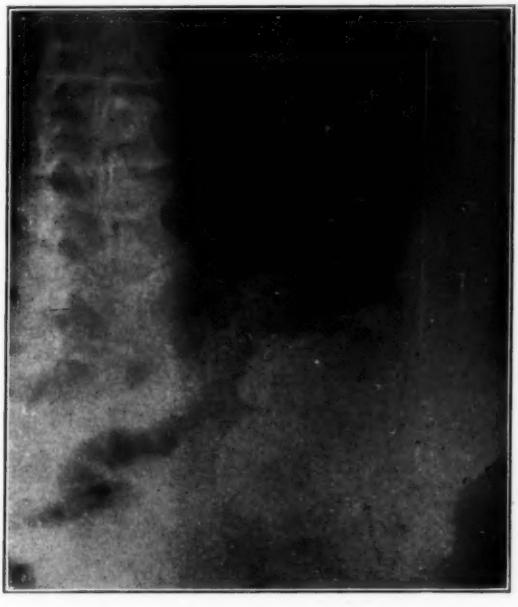

Fig. 5B. Patient R.B. Shows gradual filling up of defect 10 days after treatment.

Fig. 5C. Patient R.B. Four weeks after treatment. Note nipple-like defect.

Fig. 5D. Patient R.B. Six weeks after treatment. Note stalk-like defect.

Fig. 5E. Patient R.B. Seven and a half weeks after treatment. Note almost complete healing.

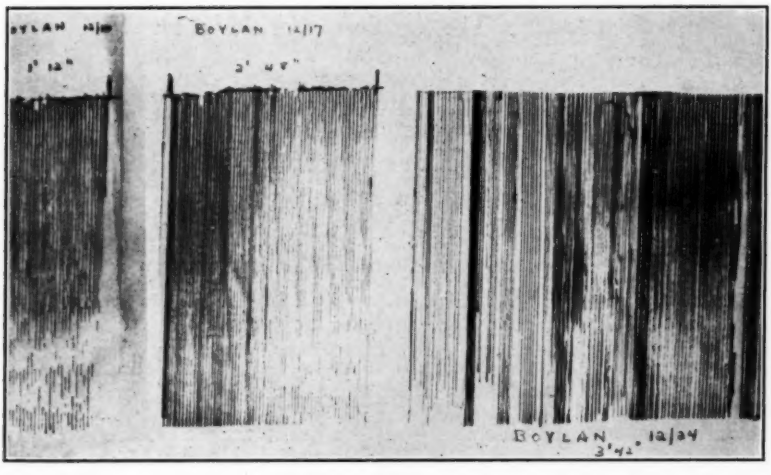

Fig. 6. Ergogram of ulcer patient C.B. Panel (a) initial ergogram, E.T. 1'2"; Panel (b) E.T. 2'48", 6 days after treatment; Panel (c) E.T. 3'42", 2 weeks after treatment.

TABLE X

EFFECT OF FEEDING MIXTURE ON pH AND FREE ACIDS IN THE GASTRIC JUICE OF A PEPTIC ULCER PATIENT

Time	*pH*	*F.A.*	*T.A.*
10:00	2.05	47.0	65.5
10:10	1.92	59.0	78.5
Feeding: 10:10			
10:45	4.21	—	205.5
11:00	4.24	—	269.5
11:15	4.15	—	245.5
11:30	4.07	—	305.0
11:45	4.22	—	298.0
12:00	4.18	—	286.5
12:15	3.68	3.0	212.5
12:30	3.01	34.5	191.5
Amigen: 51.1 g. Dextri-maltose: 58.6 g.			
Formula	5.22	—	456.0

Another feature of this treatment is that where obstructions were found in the six-hour x-ray plates, they were relieved in twenty-four hours by amigen feeding. The significance of this point will be commented on later.

The question arises: What is there in protein hydrolysate feeding which may account for these prompt results? Amigen is an amphoteric substance and the addition of it to a hyperacidic gastric juice raises the pH to almost the point of abolition of peptic activity. Table X shows that the pH of a gastric juice, originally between 1.92 and 2.05, was raised by the feeding of a mixture of 51.1 grams of amigen and 56.8 grams of dextri-maltose to 4.24. The free acid originally was reduced to zero for about an hour and fifteen minutes. After that, the pH began to decline and the free acid to rise. It is perhaps this action of neutralization of the acid in connection with the giving of a rich nutrient solution to enable the body to build up its tissue deficiency which accounts for the prompt healing in these cases. Thus it seems that by the peculiar virtue of its being both an antacid and a rich nutriment,

TABLE XI

PATIENT WITH GASTRO-JEJUNOCOLIC FISTULA FED WITH PROTEIN HYDROLYSATES

A.S. Date 1942 Feb. 29 to March 1	*N Intake*	*Nitrogen Output*			*N Bal. gms.*	*P.P. gms. % A/G*	*Wt. Kgms.*	*Remarks*
		Urine N gms.	*Fecal N gms.*	*Total N Output gms.*				
March 1	11	10.28	3.36	13.64	—2.64	5.25	47.9	Lost 15 lb.
1-2	8	9.42	4.41	13.83	—5.83			3 weeks x-ray:
2-3	9.4	8.74	4.85	13.59	—4.19	5.15	47.3	G-J-C- fistula
3-4	14.58	10.61	1.04	11.65	2.93			"Stronger"
4-5	14.58	11.38	1.03	12.69	1.89		47.8	
5-6	8.46	7.24	1.58	8.82	—0.36			
6-7	8.8	7.94	1.14	9.08	—0.28		47.3	"Weaker"
7-8	18.9	16.85	1.06	17.91	.91	5.25		
8-9	18.9	13.27	1.21	14.48	4.42			
9-10	18.9	14.08	1.47	15.65	3.25			
10-11	18.9	15.18	1.37	16.55	2.35			
11-12	18.9	15.06	1.45	16.51	2.39			
12-13	18.9	14.87	1.26	16.13	2.77			
13-14	18.9	16.48	1.48	17.96	0.94	6.1	49.1	x-ray: healed "strong"

amigen and perhaps other hydrolysates are specially suitable for the treatment of peptic ulcer.

Value of Hydrolysates: The studies in the cases of burns, gastrectomy, cholecystectomy and herniotomy show how valuable hydrolysates are in conditions in which natural food cannot be ingested or ingested only in quantities insufficient to replace increased nitrogen loss due to disease. Whereas the nitrogen intake in the natural diet is generally limited to the 20.8 grams (.34⅔ grams/KBW for a 60-Kgm. man) in the high protein diet, the intake possible with protein hydrolycates may be many times that amount. By the intravenous route, 3 liters of a 5 per cent amigen may be safely given. This is equivalent to .3 grams/KBW. By mouth, it has been found that most patients can tolerate as much as .8 grams of nitrogen per Kgm. without having diarrhea.

If both routes are simultaneously utilized, a total of 1.1 grams of nitrogen per KBW may be given, over 500 per cent of the intake possible with natural food. It is quite possible that further research in this field will make available a product which can be given in greater concentration and which will be of maximum human biological value, thus further raising the ceiling of replenishment.

However, hydrolysates have another field of usefulness. The cases of pyloric obstruction following peptic ulcer which were relieved twenty-four hours after amigen feeding, suggest that hydrolysates are better tolerated by a diseased gastro-intestinal tract than natural food. Additional evidence for this may be seen in Table XI which summarizes the nitrogen balance study of A.S., a 48-year old man who was admitted with a gastro-jejuno-colic fistula, having lost 15 pounds in three weeks. During the first three days on the natural diet, the patient was losing in the stool from 3.36 to 4.85 grams of nitrogen per day or almost half of his intake. This was accompanied by negative nitrogen balance, weakness and loss of weight. He was then put on amigen by mouth, taking an amount corresponding to 14.58 grams of nitrogen daily. This was followed by a reduction of fecal loss of nitrogen to over 1 gram and a sense of returning strength and well-being. The intake was again reduced to 8.46 for two days, at which time he was again in negative balance and feeling weaker. After that, on an intake of 18.9 grams of nitrogen, he was on positive nitrogen balance which continued for about a week, at which time the x-rays showed the fistula to be apparently healed.

We may also mention three cases of ulcerative colitis treated with amigen, in whom the nutrition was maintained although the pathological condition was not improved.

A case of pernicious vomiting of pregnancy may also be reported. A tube was passed into the stomach through one nostril and amigen feeding was instituted, at which time the vomiting stopped. This feeding was continued for three days until the nasal irritation caused by the tube became so marked that the tube had to be withdrawn. The tube was replaced in another twenty-four hours through the other nostril and a feeding period of three days was instituted. Thus a "lean" period of one day alternated with a "fat" period of three days until after four weeks the patient was able to tolerate food. The patient went to term uneventfully. This better tolerance on the part of a pathologic gastro-

intestinal tract for hydrolysates may be expected, since it is spared the task of having to take food apart and since the minimum of digestive effort is called for before absorption takes place.

One is led to speculate how worthwhile it would be to try feeding this substance in other conditions in which the gastro-intestinal tract cannot tolerate natural food, such as sprue, typhoid fever, etc.

In the use of hydrolysates one has to make sure that in the intravenous form they are not toxic, not anaphylactogenic, non-pyrogenic, and non-irritating to the site of injection. In the oral form, efforts are still being made by manufacturers to produce a good-tasting preparation and one which can be given in large amounts without causing diarrhea or vomiting. For both oral and intravenous preparations we must insist that they maintain positive nitrogen balance in the human being. Finally, the clinician who uses them must think quantitatively not only in terms of nitrogen but in terms of adequate caloric intake. Otherwise, the results will not be satisfactory.

Assay of Protein Nutritional Status: In conclusion, some general comments on the assay of the nutritional course of a convalescent patient may be pertinent. At present there are four likely methods of doing this: 1) nitrogen balance; 2) plasma protein curve; 3) body weight curve; and 4) the bedside ergograph.

Nitrogen balance determinations require a tedious and rather complicated chemical procedure not available to the average hospital. It depends for its validity on a bookkeeping process which as evidence is at best only circumstantial and not directly concerned with the effects on the body occasioned by the nutritional state.

The other three methods are more closely connected with assay of the body status. However, none of these methods is sensitive. A large amount of plasma protein could be lost from the blood without its being reflected in the plasma protein level, and hydration and dehydration can cause marked swings in the values. The body weight is also subject to the factors of hydration, to retention of urine and feces. It is inconvenient and not easily measured in the bed patient without adequate personnel.

As mentioned before, the ergograph has the theoretical objections of motivation and the learning factor. However, it has seemed to us that the changes in endurance produced by nitrogen loss are so striking that the ergograph findings transcend these two factors. The ergograph de-

terminations are sensitive enough to be of clinical usefulness, and in conjunction with the other three methods, the ergograph is a valuable tool. Serial readings of all three are more valuable than single determinations.

Summary

1. Proteins are essential to wound healing, to the maintenance of tissue integrity; and from present indications, to expeditious convalescence. Protein deficiency endangers all three.

2. A patient can become protein-deficient as a result of inadequate intake and increased nitrogen output or a combination of these two factors.

3. Decreased intake may be due to the patient or neglect on the part of the attending staff.

4. Increased output may be due to increased metabolic loss and to the loss through exudates.

5. The ceiling of nitrogen intake in natural food is naturally low and consequently natural food is often inadequate to replenish the increased protein loss in disease and injury.

6. Studies on cases of burns, of postoperative gastrectomy, cholecystectomy and herniotomy, suggest that convalescence can be shortened, strength and weight conserved by full caloric and nitrogen replacement immediately postoperatively; and that there may be a critical range of nitrogen intake for each disease category.

7. The protein hydrolysates, by raising the ceiling level of nitrogen-intake, are indispensable in many disease conditions and can be used with greater elasticity than natural food.

8. In the course of study on the value of protein hydrolysates, a new treatment for peptic ulcers has been evolved.

9. Protein hydrolysates for clinical use must fulfill a number of criteria and clinicians using them must be quantitatively-minded.

10. A discussion on the assay of the nutritional course of convalescent patients has been attempted.

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FACTORS DETERMINING THE DOSAGE OF PENICILLIN IN THE TREATMENT OF INFECTIONS*

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IT IS now well established that penicillin is an extremely effective agent for the treatment of many different types of infections, but a review of the clinical reports makes it at once evident that there is little agreement concerning the amount, or the mode or frequency of administration required to effect a satisfactory therapeutic response. Due to the scarcity of the drug there was at first a tendency to administer small amounts, and as a result erroneous impressions arose concerning the effectiveness of penicillin in diseases such as subacute bacterial endocarditis. More recently, doses found arbitrarily to give satisfactory results have been recommended by various groups of investigators. An example of the discrepancies resulting from this procedure is the recommendation, in cases of staphylococcal sepsis treated with a continuous intravenous infusion of penicillin, of 30,000 to 40,000 units daily by one group,[1] while in the opinion of others 300,000 to 400,000 units should be administered each day.[2]

Now that penicillin is readily available, it is desirable to review the laboratory and clinical experiences which have helped to clarify many of the confusing problems of dosage and mode of administration. The purpose of the present report, therefore, is to bring together the important contributions which provide a basis for rational therapy.

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Two outstanding characteristics of penicillin are its high degree of antibacterial action and its selectivity. In contrast to the sulfonamides whose action is primarily bacteriostatic, penicillin in concentrations obtained in patients causes sterilization of cultures of susceptible organisms within 24 hours and is for this reason often referred to as a bactericidal agent. Unlike true bactericidal substances such as the phenols, which sterilize cultures within a few minutes, penicillin even in high concentrations does not cause death of microörganisms unless the contact is maintained for many hours.[3] Of great practical importance, however, is the fact that both *in vitro* and *in vivo* penicillin is much more effective in its antibacterial action than the sulfonamide drugs.

Selectivity refers to the high degree of antibacterial activity obtained by penicillin against gram-positive bacteria, and its failure to inhibit the growth of the majority of gram-negative bacteria.

Variations in susceptibility to penicillin occur not only among different species of bacteria, but also among various strains of any one species. With most penicillin sensitive bacteria, however, and particularly with the pneumococcus,[4] beta-hemolytic streptococcus,[5] and gonococcus,[6] these variations are not of clinical significance since they are not of sufficient magnitude to affect the results of therapy. For this reason, routine sensitivity tests of the infecting organisms are of no practical value to the clinician in most diseases for which penicillin is employed. There are exceptions, however; for example in certain staphylococcal infections, and in patients with subacute bacterial endocarditis in which the etiological organisms may be penicillin resistant streptococci (enterococci), knowledge of the sensitivity of the organism may be of importance both from the standpoint of therapy and prognosis.

Correlation between the *in vitro* sensitivity of various organisms and clinical results obtained in patients is much closer with penicillin than with the sulfonamides. This is probably due to the fact that substances such as pus and exudate which inhibit the sulfonamides, do not impair the action of penicillin.[7] Indeed, under certain conditions, by promoting the multiplication of bacteria these substances actually seem to enhance the antibacterial action of penicillin.[8]

In view of the frequency with which various organisms acquire resistance to the sulfonamides, the problem of penicillin resistance has received intensive study. Laboratory investigations indicate that re-

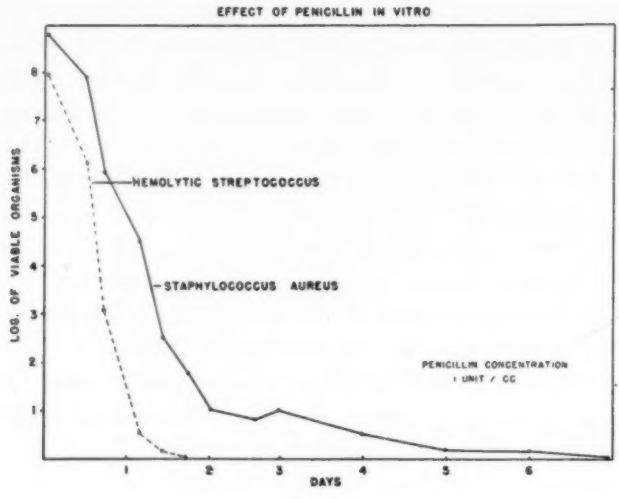


FIG. 1

sistance of the beta-hemolytic streptococcus,[9, 10] gonococcus,[11] pneumococcus,[10] and most other susceptible organisms develops only after prolonged exposure to penicillin. Clinical experience has confirmed these observations; with the exception of the staphylococcus, well substantiated instances of penicillin resistance acquired during therapy have not been described. Further, in patients with streptococcal, pneumococcal, and even staphylococcal infections, in whom relapses occurred because of the location of the organisms in relatively avascular areas, penicillin therapy has been continued for many weeks without the development of any measurable degree of penicillin resistance.[12, 13] Final conclusions cannot be drawn, but the evidence so far available suggests that, with the exception of infections caused by the staphylococcus, penicillin resistance will not become an important clinical problem.

The behavior of the staphylococcus when exposed to penicillin differs from that of other organisms. In contrast to the beta-hemolytic streptococcus, for example, whose growth is completely inhibited by penicillin in 24 to 36 hours, viable staphylococci can often be recovered from cultures for as long as 6 or 7 days (see Figure 1). Clinically, the same situation is observed in patients with empyema. In streptococcal and pneumococcal empyemas the administration of intrapleural penicillin for 1 or 2 days causes complete sterilization of the fluid, while in

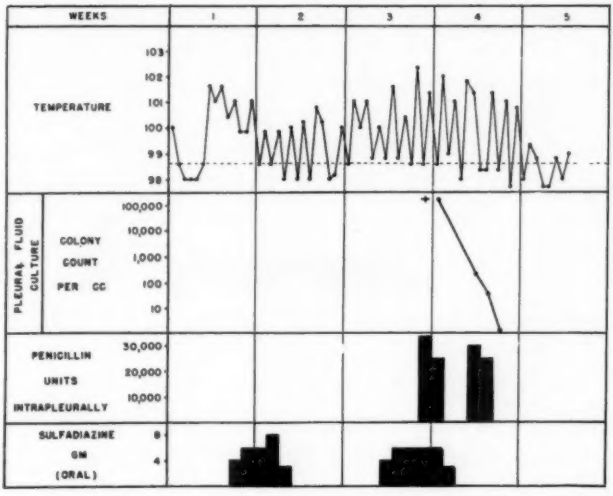


FIG. 2—Antibacterial effect of penicillin in staphylococcal empyema.

staphylococcal infections of the pleural cavity treatment must often be continued for at least a week. An illustrative case of staphylococcal empyema is presented in Figure 2. Twenty-four hours after the initial intrapleural injection of 40,000 units of penicillin the fluid contained 100,000 organisms per cc.; on the 4th day there were 100 organisms per cc.; and sterilization was not effected until the 7th day.

Staphylococci which remain viable for several days in the presence of bacteriostatic concentrations of penicillin are often penicillin-resistant, and contain an enzyme-like substance, "penicillinase", which in small quantities destroys large amounts of penicillin.[14] The relationship of this substance to other "penicillinases" has not been elucidated, but it is probable that studies of various penicillin inactivators will reveal valuable information concerning the basic structure and mode of action of penicillin. Penicillin resistance has been observed in approximately 10 per cent of strains of staphylococci isolated from clinical sources.[9, 15] Whether resistance occurs as an acquired characteristic as a result of contact of the bacteria with penicillin, or whether the sensitive organisms are eliminated leaving naturally resistant staphylococci is not definitely known, but recent studies of two independent investigators[16, 17] support the latter possibility. The evidence further suggests that re-

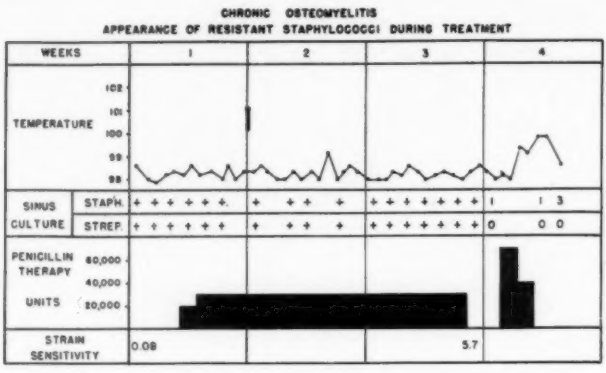


FIG. 3

sistance is much less likely to be manifested if the organisms are, from the start, kept in contact with high concentrations of penicillin. The appearance of penicillin resistance in a case of staphylococcal osteomyelitis treated with inadequate doses of penicillin is presented in Figure 3. The staphylococci isolated prior to the institution of therapy were killed by relatively low concentrations of penicillin, whereas strains isolated after two weeks of treatment with penicillin in a dose of 5,000 units every 4 hours were markedly resistant. More favorable results have been obtained in other cases receiving large doses of penicillin. Here, of course, as in staphylococcal infections in general, the necessity of prolonged therapy as well as adequate doses should be emphasized.

ABSORPTION AND EXCRETION OF PENICILLIN AND ITS DIFFUSION INTO VARIOUS BODY FLUIDS

Before considering the relationship of the concentration of penicillin in the blood to antibacterial action, it is well to review briefly studies on the absorption, excretion and diffusion of penicillin. Penicillin is most frequently administered intramuscularly, although other routes may be used. When injected into the muscle, absorption is rapid, producing maximal concentrations in the blood within 15 to 20 minutes. Beginning penicillin therapy with an initial intravenous injection is therefore completely unnecessary, although it is a common procedure, presumably as a holdover from sulfonamide medication, in which an initial intravenous injection is often advisable.

Once absorbed, penicillin is eliminated from the body very rapidly.

It was originally thought that approximately 40 per cent of the dose injected was destroyed in the body,[7, 18] but recent evidence indicates that destruction by the tissues is actually slight, and that almost all of a single dose administered intramuscularly or intravenously is excreted in the urine.[19] Eighty per cent appears in the urine within two hours, and after the fourth hour the amount remaining in the body is less than 5 per cent of the original dose. By various methods of studying renal clearance it has been definitely demonstrated that the reason for the rapid elimination of penicillin from the body is that it is excreted both by the glomeruli and the renal tubules.[20, 21]

These two factors, rapid absorption and rapid excretion, are responsible for one of the greatest disadvantages of present day penicillin therapy, namely, the necessity for frequent, parenteral injections. Intensive efforts are being made to perfect methods of delaying the absorption of penicillin, by mixing it with beeswax and peanut oil,[22] by the use of vasoconstrictors,[23] and by the application of cold compresses near the site of injection.[24] Attempts are also being made to delay excretion by combining penicillin with substances of high molecular weight,[25] and by the concomitant administration of other agents, such as para-aminohippuric acid, which compete with penicillin for excretion by the renal tubules.[26] The most promising of these methods at present is the intramuscular injection of penicillin-beeswax mixtures; blood levels are maintained for as long as 24 to 28 hours following the administration of 300,000 units of penicillin in 1 cc. of 5 per cent beeswax and peanut oil.

Methods of administering penicillin by mouth are also being studied. The best evidence at present indicates that none of the enteric coatings, oils, or antacids, so far employed give results better than those obtained with the ingestion of penicillin dissolved in tap water. With this method, five or six times as much penicillin must be administered to produce levels equivalent to those following parenteral injections.[27] The increased commercial production of penicillin, plus the fact that oral preparations do not need to be as highly purified as those used parenterally, may eventually make oral administration feasible even if methods of avoiding the destructive action of the gastric juices or increasing absorption from the intestine are not evolved.

Knowledge concerning the distribution of penicillin in the body is essential for good therapeutics. In general, diffusion of penicillin into various body fluids and cavities occurs irregularly, and to a small extent.

For this reason local therapy as well as parenteral injections have been used in the treatment of infections of pleural, pericardial and joint cavities. Frequently when the infection is well localized, as in empyemas, systemic administration of penicillin is not required, favorable results being obtained by local injections alone.[28]

With the usual therapeutic doses penicillin does not appear in measurable quantities in the spinal fluid of normal individuals, and as a result intrathecal administration is commonly used in patients with infections of the meninges.[29] More recently it has been shown that with very large doses of penicillin small amounts can sometimes be detected in the spinal fluid of normal subjects[30] and in patients with meningitis.[31] Others, however, have found that in patients with meningitis, penicillin appears in the spinal fluid very irregularly and in low concentrations.[32] Although a few patients with meningitis have been cured by parenteral administration alone,[33] clinical experience has shown that others have failed to respond to such therapy[32] and that in some cases bacterial meningitis has actually appeared during the course of parenteral treatment of extrameningeal infections.[34]

The subject is controversial, but the best evidence indicates that, for adequate and conservative therapy of staphylococcal, streptococcal and pneumococcal meningitis, both parenteral and intrathecal routes should be used. Since some strains of meningococci are relatively resistant to penicillin[35] and the results obtained with the sulfonamides are so favorable, the latter drugs should be used in the treatment of meningococcal meningitis. The one exception to the use of both intrathecal and parenteral injections of penicillin is syphilitic meningitis, in which results with intramuscular injections alone appear to be excellent.[36]

There are certan conditions, notably subacute bacterial endocarditis, various forms of late syphilis, and chronic osteomyelitis, in which another important factor must be considered, namely, penetration. Early results of penicillin therapy in subacute bacterial endocarditis, using only 5000 units every four hours, were so disappointing that for a time penicillin was abandoned for the treatment of this disease. More recently, large amounts have been administered for two to eight weeks, and a fairly large number of cases have now been reported in which the infection has been eradicated. These favorable results are presumably due to the fact that with the maintenance of high, continuous blood levels of penicillin, there is penetration into the vegetations and destruction of

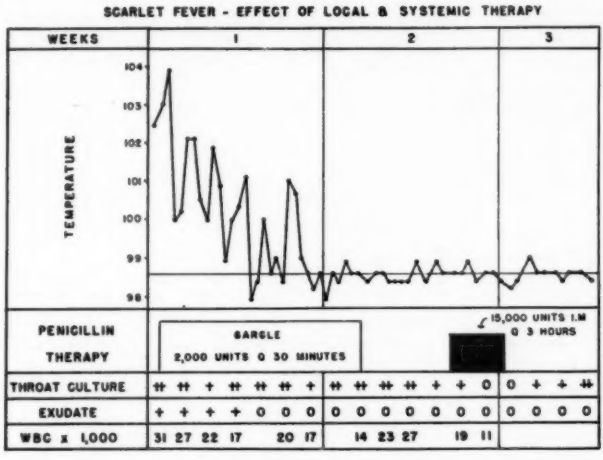


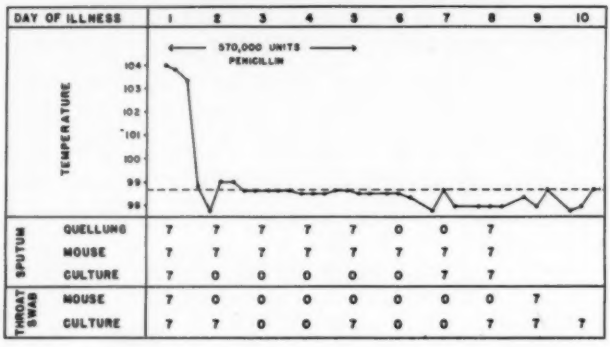
FIG. 4

organisms so that a clinical relapse is prevented. Similarly, although surgical removal of avascular areas is usually necessary in cases of chronic osteomyelitis, instances do occur in which high continuous levels of penicillin produce sufficient penetration to bring about clinical cures.[13]

The failure of penicillin to appear in the saliva of normal subjects[18] or in the sputum of patients with pneumonia[37] may be of importance in infections of the respiratory tract. A study undertaken by the Commission on Acute Respiratory Diseases to determine the effect of penicillin on the normal throat flora showed that the parenteral injection of 20,000 units every 3 hours resulted in no distinct change in the ease of isolation of beta-hemolytic streptococci, pneumococci or staphylococci from the throat. Whether this failure to eradicate organisms from the throats of normal carriers was due to (1) a failure of penicillin to cross the normal mucous membranes, (2) lack of secretion of the drug in the saliva or (3) that the susceptible organisms were present in a resting state and were therefore not susceptible to penicillin, cannot be determined.

In contrast, penicillin is highly effective against organisms in the throat of patients with tonsillitis and pharyngitis. The beneficial effects, however, are exerted only when penicillin is administered parenterally. This is well illustrated in Figure 4, in a patient treated initially with penicillin gargles in whom there was no improvement either clinically or

EFFECT OF PENICILLIN THERAPY IN PNEUMOCOCCAL PNEUMONIA



DAY OF ILLNESS		1	2	3	4	5	6	7	8	9	10
SPUTUM	QUELLUNG	7	7	7	7	7	0	0	7		
	MOUSE	7	7	7	7	7	7	7	7		
	CULTURE	7	0	0	0	0	0	7	7		
THROAT SWAB	MOUSE	7	0	0	0	0	0	0	0	7	
	CULTURE	7	7	0	0	7	0	0	7	7	7

FIG. 5

bacteriologically. The failure to obtain a favorable response by local applications in this instance was undoubtedly due to the fact that the contact between the organism and penicillin was very brief, and emphasizes the point that relatively prolonged contact is necessary. When penicillin was administered by intramuscular injection, however, the streptococci rapidly disappeared, only to reappear when treatment was discontinued after three days. It has been definitely demonstrated that in order to bring about a permanent cure in cases of streptococcal sore throat, it is necessary to continue treatment for a period of at least five days.[38]

In pneumococcal pneumonia, studies by the Commission on Acute Respiratory Diseases have shown that viable, virulent pneumococci can be recovered from the sputum during and following therapy with penicillin for as long as sputum can be obtained.[37] A representative case, showing the method of study, is presented in Figure 5. Thus, although penicillin may destroy some of the organisms present in the parenchyma of the lung, a reactivation of the infection may be caused by pneumococci remaining viable in the bronchial exudate if treatment is discontinued too soon. Clinical relapses occurring in patients treated with penicillin for only two or three days have been described by Tillett, Cambier, and McCormack.[28]

With both streptococcal pharyngitis and pneumococcal pneumonia, then, it is necessary to continue treatment for several days to insure sterilization of the infected tissues and prevent relapses. It would appear that penicillin merely inhibits growth of the bacteria, thereby localizing

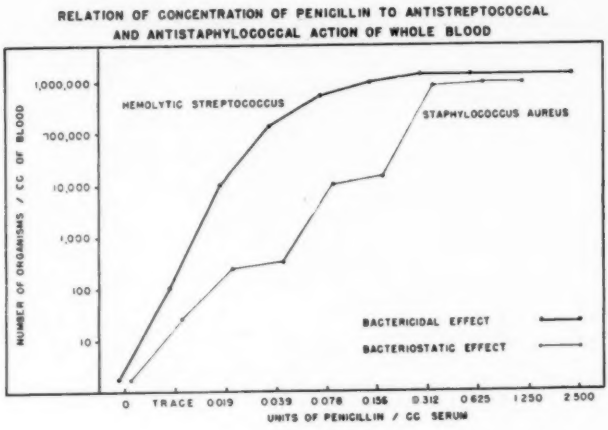


FIG. 6

the infection; actual recovery is brought about by the body's own defense mechanisms. The development of natural immunity is probably of importance also in conditions other than pneumonia and pharyngitis, but so far these relationships have not been worked out in detail.

RELATION OF BLOOD CONCENTRATION TO ANTIBACTERIAL ACTIVITY

Ideally, the objective of therapy with penicillin, as with other chemotherapeutic agents, should be to maintain, at the site of the infection, concentrations of penicillin which exert maximal antibacterial activity throughout the entire period of treatment. From a practical standpoint this is not feasible at the present time, and is even considered disadvantageous by some observers,[39] on the basis that since penicillin is effective against bacteria only during the stage of multiplication, intermittent therapy will allow periods of multiplication alternating with periods of bacteriostasis, and will therefore be more effective. This objection to continuous therapy, based on *in vitro* observations, does not take into consideration conditions existing locally in the tissues, and from a practical standpoint the results obtained clinically with continuous effective concentrations of penicillin in the blood stream are excellent. Indications are that in the future penicillin will be administered by methods which will provide constant measurable blood levels.

In vitro tests of whole blood obtained from normal individuals receiving penicillin have shown[40] maximal antibacterial activity against

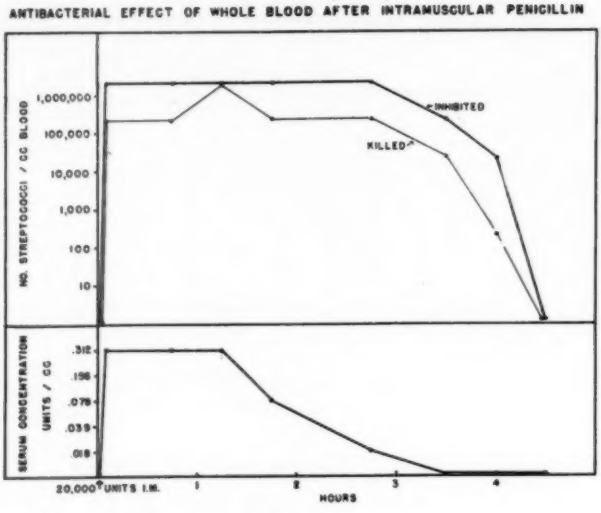


FIG. 7

hemolytic streptococci and staphylococci by concentrations as low as 0.04 and 0.2 units per cubic centimeter respectively (Figure 6). Lower concentrations exhibit definite, but not maximal activity; higher concentrations do not produce any appreciable increase in antibacterial action. These values, 0.04 and 0.2 units per cubic centimeter, which apply respectively to a highly sensitive and relatively resistant organism, are of fundamental importance in relation to the concentrations obtained in the blood stream of patients.

Since chemical methods are not available, penicillin assay methods in use at the present time are based on the ability of penicillin to inhibit the growth of sensitive microörganisms. One of the defects of these methods is their inability to detect small concentrations of penicillin in body fluids. The smallest concentrations which can be measured accurately, 0.02 to 0.04 units per cubic centimeter, are highly effective against most penicillin sensitive bacteria, and it is important, therefore, to have some knowledge of how long penicillin exerts therapeutic action in the body after it can no longer be detected in the blood stream.

Bactericidal tests of whole blood obtained from patients during and following therapy have revealed valuable information on this subject.[40] In patients receiving intramuscular injections of 20,000 units, the bac-

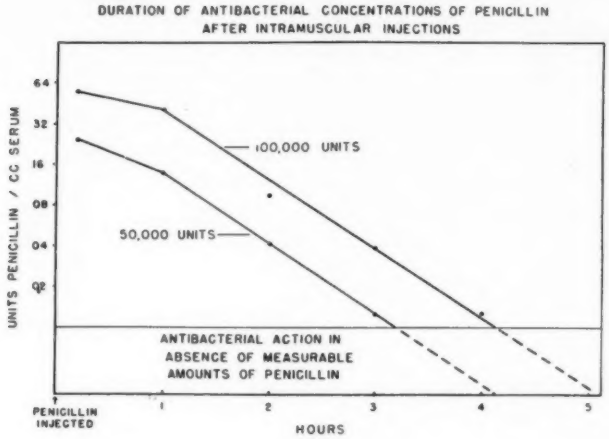


Fig. 8

tericidal power of the blood was found to be increased for a period of from 30 to 75 minutes after penicillin was no longer detectable in the serum by routine assay methods. This is illustrated in Figure 7. From this evidence, it would seem highly unlikely that, following the usual injection of 15,000 to 20,000 units, one could count on any therapeutic activity for more than one hour after detectable levels were no longer present. Since with these doses penicillin is present in measurable amounts in the blood stream for from two to three hours, it can reasonably be assumed that, for all practical purposes, therapeutic activity will cease between the third and fourth hour. These observations are supported by the evidence alluded to previously, indicating that by the end of the fourth hour all but about 5 per cent of the dose administered is excreted in the urine.

A point of interest in this connection is the effect of an increase in the size of the dose upon the duration of therapeutic activity in the blood stream. This is illustrated in Figure 8, in five patients who received single intramuscular injections of 50,000 units, and at a later date additional injections of 100,000 units. Doubling the size of the dose produced blood concentrations twice as high as those observed with 50,000 units, but the duration of assayable blood levels was prolonged by only about one third. This relative inefficiency of larger doses, also pointed out by Fleming,[41] has the additional disadvantage of producing

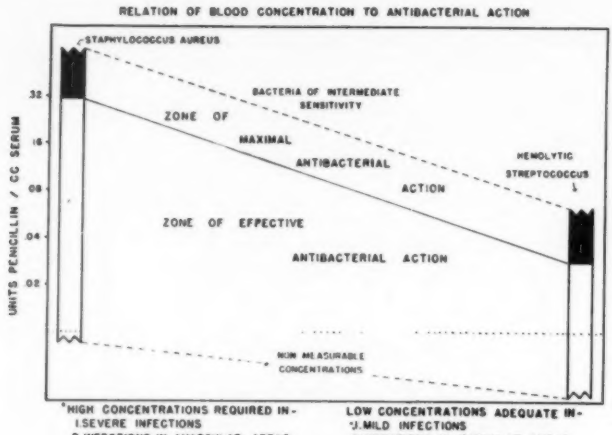


FIG. 9

levels in the blood stream which are considerably in excess of those necessary to exert maximal bacteriostasis.

The broad relationships of the concentration of penicillin in the blood stream to the sensitivity of various susceptible organisms, as well as to other factors, are summarized diagrammatically in Figure 9. The extremes of variation in susceptibility are represented by the staphylococcus and the hemolytic streptococcus. In addition to the staphylococcus, many strains of Streptococcus viridans and non-hemolytic streptococci should be included in the resistant group. Because of the serious nature of infections such as syphilis, diphtheria, and gas gangrene, the organism causing these diseases should also be regarded as highly resistant from a therapeutic standpoint until more information is available concerning their susceptibility both *in vitro* and *in vivo*. Organisms other than the hemolytic streptococcus which may be considered highly sensitive are the gonococcus and pneumococcus. Strains of intermediate sensitivity are represented by the meningococcus. The relative susceptibility of various other organisms, including fungi, spirochetes, and rickettsiae are not definitely known.

Other factors of importance in determining the size of the dose of penicillin are the severity of the infection, the vascularity of the area involved, and the barriers through which penicillin must diffuse or penetrate in order to come into contact with the infecting organisms.

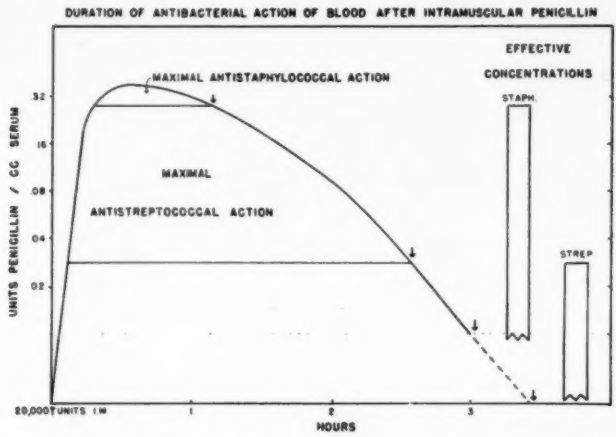


FIG. 10—Arrows indicate time that subsequent injections of penicillin are required to maintain the indicated degree of antibacterial action.

The zone of maximal antibacterial action includes concentrations of penicillin which will cause complete inhibition of growth of the bacteria, and which should ideally be maintained throughout the entire period of treatment. However, definite bacteriostasis is exerted by concentrations considerably lower than those regarded as maximal. As indicated on the chart (Figure 9), this zone of effective antibacterial action includes, for highly susceptible organisms, concentrations of penicillin lower than those which are measurable by present methods of assay.

The relationship of these zones of antibacterial activity to blood levels obtained with intramuscular injections of penicillin in saline is presented in Figure 10. An injection of 20,000 units produces levels in the blood stream considered maximal against the staphylococcus for a period of less than one hour, and levels which are definitely bacteriostatic, although not maximal, for another two hours. For the hemolytic streptococcus, on the other hand, the same dose of penicillin produces concentrations having maximal antistreptococcal action for a period of more than two and one-half hours, with partially inhibitory levels for another one and one-half to two hours.

From these figures it is possible to plan rational schemes of therapy for various infections taking into consideration in addition the factors presented in Figure 9. For staphylococcal infections, for example, injections of 25,000 units every two hours will produce optimal continu-

ous levels in the blood stream; for streptococcal infections, 15,000 units every three hours are adequate. It is not within the scope of this paper to make specific recommendations of dosages for various types of infections; the examples cited are presented merely to illustrate the manner in which the dosage schedules are evolved.

The blood concentrations listed in Figures 9 and 10 may also be attained by continuous subcutaneous, intramuscular, or intravenous infusions of penicillin. Although somewhat tedious, these methods of administration are often desirable for the initial treatment of patients seriously ill from overwhelming infections. Blood levels which can be more or less constantly maintained with a continuous intravenous infusion for twenty-four hours are as follows: with 100,000 units, 0.1 unit per cubic centimeter, with 200,000 units, 0.2 unit per cubic centimeter, and with 400,000 units, 0.4 unit per cubic centimeter.[21] With a continuous intramuscular infusion, the levels are almost identical with those obtained by the intravenous route.[34] Subcutaneous administration, however, produces concentrations only about one half as great as those observed with the other two methods.[21] Daily dosages adequate for various types of infections may be ascertained by reference to Figure 9.

Two points require special emphasis. One is that doses producing optimal concentrations of penicillin in the blood stream are all that are necessary. Giving larger doses merely raises the concentration of penicillin, without increasing the already maximal antibacterial activity. This point is reiterated with the hope that it will temper the present tendency towards overdosage which, while not harmful to the patient, is wasteful and unnecessary.

The other point is that, for all practical purposes, penicillin remains active in the tissues for only three or four hours following the usual therapeutic doses. Penicillin is often administered only four times a day, leaving a period of twelve hours during which no injections are given. Results obtained with this regimen are so favorable in diseases such as pneumococcal pneumonia[28] that there is considerable speculation about the possibility of antibacterial activity remaining in the tissues for many hours after penicillin has apparently left the blood stream. From the data presented in this paper it would appear that this assumption, the implications of which are potentially dangerous, is entirely erroneous.

In conclusion, it must be stated that the exact blood concentrations presented in Figures 9 and 10 cannot be regarded as final from a thera-

peutic standpoint since they are based largely on laboratory observations. Certain factors existing in the tissues, such as the activity of the leukocytes, and the various growth phases of bacteria, are poorly understood, and may eventually alter some of our present concepts. Extensive studies, both clinical and laboratory, will be necessary before a final answer can be reached. For the present, however, the data which are presented are based on sound fundamental observations, and provide a basis for the clinical administration of penicillin which is essentially conservative and rational.

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SHOCK THERAPY OF PSYCHOSES: EVIDENCES FOR AND AGAINST DAMAGE*

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A VAST literature has accumulated on this subject, which has been studied in all civilized countries of the world. This literature has been reviewed several times by able writers, but it still piles up well in advance of any possibility of dealing with it adequately. However, I shall attempt to present the subject as fairly as possible from several different viewpoints, selecting supportive evidence from a number of available sources.

There are a great many foci of special interest from the viewpoints of the various scientific and clinical disciplines. To mention a few examples, the internist, physiologist and pathologist are interested in studying the bodily organs including the brain (the particular realm of the neuropathologist) during and following the therapeutic procedure; the neurologist and neurophysiologist find their special problems in the behavior of the nervous system under this type of bombardment; the biochemist sees many opportunities to investigate what is taking place in the metabolic processes; the physicist is interested in matters of techniques particularly those involved in electro-physics; and the psychiatrist and psychologist, within whose own territory the whole business is going on, and who must assume the task of evaluating all results in terms of the mental behavior. I nearly omitted the surgeon who has to step in occasionally to patch up the bony structures when the framework yields to the strain.

Although a lot of work has been done, the various reports are difficult of evaluation as there is no uniformity in the diagnosis of mental conditions which in themselves are often not clearly differentiated syndromes; the course and outcome of any patient's case are unpredictable with or without special treatment, and usually controls that are scientifically satisfactory have not been utilized.

* Given February 16, 1945 at The New York Academy of Medicine in the Friday Afternoon Lecture series.

A number of different "shock" therapies have been tried out but the insulin, metrazol and electroshock methods and various modifications of these have dominated the picture. They are the only ones we can undertake to review here, and we shall start with a condensed account of the present concensus on the insulin method.

The indications usually mentioned are the catatonic, paranoid, hebephrenic and simple forms of schizophrenia (these are given in the order of favorable prognosis). Some workers prefer the insulin method to the convulsive ones for other acute and chronic forms of mental disorder. The shorter the duration of the illness the more favorable the prognosis, and those patients who have made a fairly satisfactory life adjustment up to the age of twenty-five or above, and whose disorder is an acute episode, have the best remission rates. Patients under the age of sixteen years show a low remission rate.

In the numerous reports available emphasis has been placed on a number of physical contraindications including coronary disease, severe myocarditis, valvular disorder, cardiac arrhythmia due to organic reasons, tuberculosis, organic impairment of the liver, kidneys or pancreas, and serious endocrine dysfunctions.

A wide variety of complications arising during the treatment itself have been described. Of these may be mentioned particularly auricular fibrillation and gallop rhythm of the heart, myocardial failure, coronary occlusion, aspiration pneumonia, laryngospasm, pulmonary edema, central respiratory failure, asthma, urticaria, aphasia, hemiparesis, and fracture and dislocations of bony structures.

Insulin therapy, according to practically all reports, increases very definitely the percentage of remissions and although many relapses occur, even in these, the patients have a period of better mental health which may allow them to reside outside a hospital. Moreover, it shortens the illness in many of those who might eventually recover spontaneously. The mortality due to the therapy itself, as reported, is less than 1 per cent.

A number of interesting studies have been made of which we have space to mention a few. One of these was made by Bond and Rivers[1] who treated 251 schizophrenics with insulin. This investigation revealed that 138 or 54 per cent were recovered or greatly improved at the end of the treatment; forty-nine of these cases were followed for five years. Of these 22 or 41 per cent had maintained their status. These cases were

compared with 100 control cases, the latter showing only a 16 per cent recovery rate at the end of a five-year period. Bond gained the impression that the quality of the remissions was much superior to that attained in the patients not so treated. There are definite criteria that could be set up to determine this point with certainty. It is possible that with the rather rapid relief from emotional tension experienced by the patient under shock therapy, his compensatory forces are freed more quickly and can work more rapidly towards a reconstruction of the defenses and adjustments than is possible by means of the slower "spontaneous" recovery process.

Gold,[2] by means of injections of mecholyl chloride, a choline derivative which stimulates the parasympathetic part of the autonomic nervous system rather specifically and by means of which one can unbalance the whole system, was able to study the autonomic balance of schizophrenics before and after insulin shock therapy. Mecholyl chloride produces a temporary lowering of the systolic and diastolic pressures, an increase in pulse rate, flushing of skin, and an increase in salivation, lacrimation and perspiration. In clinically improved patients there was a definitely increased ability on the part of the autonomic nervous system to maintain its balance, and also a more rapid compensatory reaction towards restoration of balance when it was disturbed. The activity of the sympathetic system was improved in particular.

According to Rennie[3] the "administration of insulin in subcoma doses provides an effective method of sedation. Its specific action seems to be in alleviation of anxiety. With the relief of anxiety, the psychotic manifestations sometimes rapidly disappear. The method is entirely safe and is far superior to that achieved by chemical sedation." It should be combined with organized psychotherapy.

In inexperienced hands insulin therapy is a risky procedure. Owing to the reports of various types of hemorrhage during treatment Freed and Wofford[4] suppose that there is some damage to the walls of the capillaries of the nature of an anoxemia which produces an increased permeability. Such lung complications as bronchopneumonia, lung abscess and pulmonary edema have been reported by a number of writers. Pulmonary edema in the setting of cardiac failure and insufficiency is a symptom that renders the therapist particularly uneasy (O'Neill[5]). Allergic symptoms may appear (Hinko et al[6]) in the form of decrease in tolerance, local reactions, and as an immediate anaphylactic reaction

indicating appropriate treatment instanter.

From the standpoint of the internist, prolonged coma is the most serious of all complications. If the patient does not awaken within thirty minutes after the glucose feeding, the physician should start to do something about it. Instances of prolonged coma have persisted for hours, days or weeks. There may be a high temperature, rapid pulse and respiration, and vomiting and death. Lester[7] studied twenty-five cases of prolonged coma and reported the mortality rate to be 16 per cent. After considering all reported statistics he thought that a prolonged coma occurs once in every 1,877 treatments.

Different subjects vary a great deal in their susceptibility and response to similar doses of insulin, and also the effects of low blood sugar levels vary widely in different people. These aspects have been discussed by a number of authors. One particularly interesting case was reported by Rivers and Elliott.[8] This patient "received up to 1200 units of insulin intramuscularly and up to 2500 units intravenously without going into deep stupor. Insulin produced the same total fall in blood sugar" as in those who go into stupor.

The brain is unlike other organs of the body in that it can use only carbohydrate. The brain metabolism is therefore depressed in hypoglycemia. In the convulsive therapies the respiratory movements are interfered with and the brain, as well as other organs of the body, is temporarily deprived of oxygen.

Patients receiving insulin shock therapy reveal a progression of symptoms in a caudal direction. These symptoms seem to present themselves in five groups, each one representing a different phyletic region of the brain, namely cortical, subcortico-diencephalic, mesencephalic, upper medullary and lower medullary. According to the researches of Chesler and Himwich[9] the order of progression in the depletion of glycogen from the various parts of the dog's brain under the influence of intense hypoglycemia is similar in order of structures, with one exception; in the dog the caudate nucleus is depleted before the cerebral cortex. In these animals the decrease in glycogen concentration "occurred in a definite order which with the exception of the cerebral cortex had a rostral to a caudal progression. The concentrations in the caudate nucleus and in the corpora quadrigemina decreased first, followed by those in the cortex, the thalamus, the cerebellum and the medulla. The values for the cord were never significantly below the normal."

The indications for the application of convulsive therapy (metrazol or electro-shock) are involutional states, manic depressive psychoses, and other depressive reactions. Convulsive therapy has also been used rather freely and successfully in acute catatonic episodes.

The contraindications are said to be advanced arteriosclerosis and hypertension, auricular fibrillation, cardiac dilatation, recent coronary occlusion, hyperplastic or degenerative skeletal disorders, tuberculosis, seropositive syphilis, and pregnancy. The most frequently seen complications engendered during the treatment are subconjunctival hemorrhages, aspiration pneumonia, pulmonary abscesses, auricular fibrillation, cardiac dilatation, vasomotor collapse, embolic fractures and dislocations of the bony framework, status epilepticus and memory disturbances.

Kolb and Vogel[10] estimated a death rate of 0.05 per cent in 7207 cases treated with electric shock, while Impastato and Almansi[11] placed it at 0.8 per cent in 11,000 cases.

As far as the mortality rate with the shock therapies is concerned, it is probably considerably higher than has been reported statistically. Deaths due directly or indirectly to these methods must occur here and there all over the country in places where they are not collected into reports and published in the medical journals.

Death is usually due to some other organ than the brain—and in some instances the autopsy fails to reveal the cause of death. Sometimes the cause of death is a hyperpyretic state associated with status epilepticus.

In comparing the two types of convulsive methods it may be said that metrazol is a respiratory stimulant while electro-shock is a respiratory depressant. The memory loss, with electro-shock is greater and more prolonged than with metrazol but electro-shock is easier to administer, less time-consuming, and the convulsions are less severe. Therefore, with metrazol the danger of fractures is greater. The memory and fear of the treatment with metrazol is disturbing to most patients. The "missed" convulsions usually create a great deal of anxiety. With the electro-shock method there are no "missed" convulsions, usually no memory of the treatment, and much less anxiety.

Although the prognosis after metrazol is quite favorable for manic depressive psychoses and rather high for involutional depressions, the majority of workers consider the prognosis of all these conditions to be somewhat better following electro-shock. Schizophrenics with psycho-

neurotic elaborations have an unfavorable prognosis with all methods of shock therapy.

In the application of the electro-shock treatment the effect does not depend upon the strength of the electric current but upon a successful convulsion. As far as the number of electrically induced convulsions is concerned, to produce favorable results, it is recommended that from 8 to 20 treatments usually suffice for depressions except in the paranoid involutional types which may have to be given some additional ones. Manics are given up to 20 treatments with some workers advocating as high as 2 to 3 convulsions per day instead of the usual twice or thrice weekly fits, and schizophrenics often need from 20 to 50 treatments to bring the desired results.

Smith and co-workers[12] in a follow-up study after 2 years experience with electric shock therapy which included 279 patients were impressed with its value in involutional melancholia and manic depressive psychosis. According to this report "manic patients do not hold their recovery as well as those who have an agitated depression. There is no evidence to indicate that electro-shock treatments may prevent future psychotic attacks nor that they might interfere with spontaneous recovery." They were not favorably impressed with the results in schizophrenia and thought this type of therapy of doubtful value in psychoneurotic conditions. Intocostrin (Squibb) was used to decrease the incidence of traumatic skeletal injuries.

Combined convulsive therapy and psychotherapy has been advocated by some authors including Moriarty and Weil[13] but the majority of experienced psychiatrists have not been impressed with the results in the neuroses as far as the shock therapy part of the contribution is concerned. To me the distinction between a psychosis and a psychoneurosis is not a theoretic matter of controversy nor merely an academic exercise. The patterns of the two groups of disorders are different, although it may often require a deep and prolonged study of a given case to reveal the differentiating points as quantitative factors as well as qualitative ones are to be considered.

Favorable results with the electric shock method have been reported extensively and rather consistently, but there are still questions in the minds of some regarding physical complications. Most of the accidents reported are considered to be minor in nature. Some of them can be prevented by the use of curare[14] or by the proper position of the body.

Unless there is a universal tendency to emphasize the favorable results and to minimize the untoward ones, patients are rarely made worse psychiatrically although Kalinowsky and Worthing[15] say that "deeply regressed but quiet patients may become chronically disturbed."

The recovery course is not always smooth. Certain reactions have been pointed out by Osgood[16] as examples. Not infrequently "when the memory clears the depressed mood tends to return, particularly where there are unpleasant situations to be faced; or sometimes the pendulum swings too far and the depressed patient becomes hypomanic, or perhaps the memory does not clear up quickly and the patient fears that the treatment has done him permanent harm."

Some patients do not regain their complete memory after many months. Is it possible that some never attain their original memory-power status?

Osgood[16] in his review of 357 patients treated by electric shock noted panic reactions and perseverative speech in the treatment room and also later reactions such as increased restlessness and agitation, dazed retardation, and states of excitement with uncoöperativeness.

It is possible that the "inner life of the person, which may be considered to be the core of the personality, is resistant to the impact involved in shock treatment. The improvements that do take place appear to be limited, so far as is indicated by the results of the Rorschach test, concerned with outer activities, those at the periphery of the personality. Shock therapy is not as effective in reaching the inner personality as either spontaneous remission or deep searching intensive psychotherapy. . . . Schilder made the point that the patient himself is not really reached by shock treatment,"[17] a point which my own experience supports without the slightest doubt. The matrix of the psychosis is not changed, but only the secondary, presenting features. After the most distressing symptoms are removed or modified favorably, the compensatory resources of the patient may aid him in reconstruction. "Clinical changes are associated with greater docility as a result of blunting of the emotional and intellectual life."

Electroencephalographic changes occur during the course of treatment (electric shock) and correlate with amnesia or other evidence of impaired mental function. Where there is no evidence of impaired mental function and no electroencephalographic alteration, clinical improvement does not occur.

If there is little change in the personality except in the intellectual sphere and if the gain which consists of increased intellectual control is at the expense of the total intellectual function or capacity, then perhaps shock treatment effects clinical improvement by impairing the mind of the patient. Is clinical improvement correlated with more or less permanent damage rather than being the result of temporary cerebral anoxia and stimulation of the autonomic mechanisms?

Permanent or temporary alterations in the electroencephalogram following metrazol shock therapy have been reported by Davis and Sulzbach,[18] Finley and Lesko,[19] Polatin and co-workers,[20] Levy and associates,[21] and by Knott and co-workers.[22] These authors concur generally that a large number of convulsions will produce electrocortical potentials of high amplitude and low frequency. Knott and his associates[23] in studying electroencephalographically twenty depressed patients given metrazol shock therapy observed: "(1) no significant group variation in alpha index following metrazol shock therapy although there were striking individual changes, (2) there was significant variation in slow activity after such therapy, (3) this variation was made manifest as an increase in activity of less than 6 per second frequency in the motor and frontal areas, (4) there was evidence that the amount of slow activity following therapy was conditioned by the amount of such activity preceding therapy, (5) there was individual susceptibility to change in slow wave activity."

These same workers studied also the changes in the electroencephalogram following insulin shock treatment and found an increase in the alpha index in 8 of the 10 schizophrenic patients studied. This was more prominent in the frontal areas. There were no notable uniform durations in slow activity.

In an experiment by Stainbrook[24] a group of 28 rats learned a maze under the usual hunger motivation. Then some of them were given one electro-shock daily for thirty days. When all the animals were tested in the maze twenty days after the shock routine had been terminated, both the relearning time and the relearning error scores were definitely greater than the corresponding scores of the control animals. It is perhaps significant that the re-learning error scores of the experimental animals were about the same as they were in the initial learning experience. This author pointed out the possibility that the errors in re-learning might be due to some emotional conditioning induced by shock experience,

and that this should be considered before concluding that there had occured an "enduring disorganization of the purely discriminative cognitive structural-trace of a recent maze habit." It is possible, if not probable, that this phenomenon in the rat corresponds to the memory difficulties noted in patients during and following the therapy.

Although subconvulsive shock therapy has been advocated by some workers it was found to be practically valueless by Gottesfeld and his associates.[25] In their series of twenty-four cases of affective psychosis none were improved and many of them showed fear and apprehension as a result of their experiences under the subconvulsive technique. No case of schizophrenia showed any improvement. However, Plattner and Löhnis[26] reported good results in a number of depressions particularly in those of the senile and arteriosclerotic group where the weaker currents were tolerated better by these aged and fragile persons.

The problem of circulatory failure has been presented by a number of writers. Jetter[27] concluded that there were at least two mechanisms to consider by which fatal circulatory failure could occur, i.e., an acute cardiac dilatation brought about by the muscular exertion of the convulsion; or by means of the electrical stimulation of hyperexcitable central cardiac or vasomotor centers. He reported the deaths of three patients from circulatory failure: Of these two had advanced arteriosclerotic cardiac disease and the other an acute myocardial condition. These are mentioned here to emphasize that there are hazards of this character in this field that one should take fully into consideration during the selection of patients.

A number of histopathological researches have been carried out on brain tissue. Lidbeck[28] concluded from his studies on the dog that therapeutic electric shock is not contraindicated in the therapy of psychoses. No correlation was found between the amount of current used and the brain changes which were minimal.

Horses and dogs are killed with relatively small charges of electricity as contrasted with rabbits and rats which are rather resistant [Jaffé[29]], and human beings vary a great deal in their sensitivity to electric currents.

The earlier experiments on animals were with lethal or sublethal or maximum charges and therefore the resulting brain changes should have been expected.[30] Even then they have not been too startling although they were the result of "acute experiments." Gross petechial hemor-

rhages of the meninges, capillary injection, microscopic hemorrhages, with swelling and demyelinization of the axis cylinders, gliosis, degeneration of nerve cells, vacuolization of oligodendroglia and white matter have all been described in experimental animals.

In a very painstaking neuropathological research on cats to determine the significance of the intracerebral vascular reaction Alexander and Löwenbach[31] discovered a number of interesting things which we cannot spare the time to discuss here, but among their conclusions one finds the following pertinent statement. "With single shock doses within the range of amperage used in electro-shock treatment in man, no pathological changes of the neural parenchyma could be produced which were recognizable with present-day histological methods at times varying from 4 minutes to seven days after the shock. It is concluded that early organic physiological and physico-chemical changes of the neural parenchyma must nevertheless exist, but that they are of an order not yet demonstrable morphologically. The nature of these early physiological and physico-chemical changes awaits future investigation. The question of late changes is likewise uninvestigated and open to future study."

Practically the same conclusions were reached by Winkelman and Moore[32] who also utilized cats in the experiments. Their careful histologic studies of the brains and cords failed to show any morphologic changes in the animals receiving convulsive doses analogous to those given to humans. Excessive doses do have some tendency to produce congestion and small hemorrhages. Winkelman and Moore suggest that in many experiments reported (1) the intensity of the current which produces lesions in experimental animals may be excessive as compared with that used in human therapy, and (2) the animals may have metabolic, nutritional, disturbances or lack of certain vitamins such as B, C, or K during the course of the experiments.

Heilbrunn[33] concluded from his rat experiments that the electric current as such was not responsible for the hemorrhages in the nervous system which resembled those described previously by Alpers and Hughes[34] and by Heilbrunn and Weil[35] since such demonstrable lesions occurred in the animals in which ether had been used to prevent the convulsion. This investigator was inclined, therefore, to attribute the occurrence of hemorrhages to changes in dynamic pressure associated with the muscular contractions and their attendant blood vessel changes.

Preparatory treatments with atropine, calcium, vitamin K, and a suspension of brain substance were ineffective as protection against the pressure reactions.

Hemorrhages were found in the pia arachnoid and also in the brain substance. Those in the meninges were most frequent over the base of the brain where congestion of the vessels was also prominent. Hemorrhages into the brain substance were noted through the cortex of the hemispheres, in the hypothalamic area, in the cerebellum, and particularly in the medulla and pons. With few exceptions they were petechial in type, and as they were found to be in different stages of progressive organization this indicated that some of them had occurred at the beginning during the early treatments. The group of animals having the true convulsive seizures, rather than mild attacks. revealed the most extensive and numerous hemorrhages.

It has been demonstrated that the cellular constituents of the blood are increased after convulsive treatment and chemical studies have shown that amino acids, cholesterol, vitamin C, reducing substances, oxygen, total phosphorus (organic phosphorus, acid soluble phosphorus, inorganic phosphorus), chlorids, sodium, potassium, calcium and magnesium as well as the icteric index were altered in amounts after treatment. Increases were more frequent than decreases excepting the amino acids which were decreased more than twice as frequently as increased (Katzenelbogen). Carbon dioxide was decreased after nearly all treatments, Katzenelbogen[36] suggests that this would seem to indicate hyperoxemia rather than anoxemia which has been stressed by several writers.

Since many of these constituents return to normal or become subnormal after a few hours the changes may be due to dehydration. Fluids leave the blood stream while the less diffusible substances remain. There is an increased mobility and acidity of the stomach.

Conclusions

Taking everything into consideration and after analyzing the mass of literature that has accumulated on the shock therapies, one is convinced that they have a definite place in the practice of psychiatry when they are applied by the properly qualified physician possessing the clinical sense, experience and judgment necessary to manage a psychiatric problem. Owing to unexpected complications which may develop at any time patients should always be treated in a hospital setting or at home

with the proper medical and nursing facilities. They should not be treated in the offices of physicians nor in outpatient clinics to be turned loose on the street following the therapy. The greatest advantage of the insulin method seems to be in its effect on schizophrenia, while the convulsive therapy methods are found to be the applications of choice in the affective conditions in whatever setting they have developed.

At the Psychiatric Institute monkeys subjected to electric convulsions similar to those given to humans therapeutically were studied for brain lesions. The few changes noted were found in the brains of the control animals. Therefore whatever their source might have been it was not the result of shock therapy.

Most of the vertebral farctures noted are of very little clinical importance, but are chiefly of roentgenographic significance—frequently rather indistinct in nature.

The evidence all the way through this multiphasic problem indicates clearly that the reported therapeutic results are influenced by the subjective bias or attitude of the investigator, by the adequacy of the shock therapy itself, and by the possible effect of such adjuvant measures as psychotherapy, physiotherapy, etc. Moreover, the degrees of "remission" remain to be defined in a way acceptable and utilizable by the workers. Until these factors are recognized and adjusted universally the total situation will remain difficult to evaluate.

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SEPT. 1, 1895—SEPT. 25, 1945

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APRIL 16, 1876—APRIL 25, 1945

BYRNE, JOSEPH
MARCH 21, 1870—MAY 13, 1945

CANNON, WALTER BRADFORD
OCT. 19, 1871—OCT. 1, 1945

CONAWAY, WALT P.
JUNE 17, 1872—JAN. 12, 1945

DARLINGTON, THOMAS
SEPT. 24, 1858—AUG. 23, 1945

DAWSON, MARTIN H.
AUG. 6, 1896—APRIL 27, 1945

ECKERSON, EDWIN B.
NOV. 15, 1905—APRIL 28, 1945

FISCHER, LOUIS
NOV. 21, 1864—APRIL 9, 1945

FRIESNER, ISADORE
JULY 25, 1874—SEPT. 8, 1945

GOODMAN, CHARLES
JUNE 14, 1871—MAY 23, 1945

HARROP, GEORGE A.
1890—AUG. 4, 1945

HERRICK, WILLIAM WORTHINGTON
FEB. 19, 1879—JUNE 1, 1945

HURD, LEE MAIDMENT
DEC. 23, 1873—MAY 15, 1945

JELLIFFE, SMITH ELY
OCT. 27, 1866—SEPT. 25, 1945

KEDEY, CHARLES G.
JUNE 23, 1863—SEPT. 7, 1945

KOPLIK, LEWIS HENRY
SEPT. 29, 1903—JULY 22, 1945

LEVIN, ISAAC
NOV. 1, 1866—JUNE 19, 1945

LEWIS, SIR THOMAS
1881—MARCH 17, 1945

LINDER, WILLIAM
JULY 4, 1874—AUG. 11, 1945

MALCOLM, PERCY E. D.
OCT. 9, 1870—AUG. 13, 1945

MARTIN, THOMAS A.
JUNE 9, 1873—JAN. 5, 1945

MEEKER, HAROLD DENMAN
JUNE 11, 1875—MAY 26, 1945

OFFENBACH, ROBERT
JUNE, 1859—FEB. 8, 1945

SCHWARZ, HERMAN
NOV. 28, 1861—MAY 19, 1945

SILVER, HENRY MANN
MAR. 2, 1851—SEPT. 27, 1945

SMITH, DORLAND
APRIL 29, 1875—FEB. 25, 1945

TILTON, BENJAMIN TROWBRIDGE
JULY 17, 1863—SEPT. 23, 1945

TOMS, S. W. SPENCER
DEC. 11, 1861—AUG. 22, 1945

TRUESDELL, EDWARD D.
1880—JUNE 12, 1945

VINEBERG, HIRAM
1857—MAY 4, 1945

WEISSBERG, MORRIS
FEB. 23, 1887—MARCH 17, 1945

WILSON, MARGARET BARCLAY
AUG. 28, 1863—OCT. 6, 1945

INDEX, 1945

Accessions to the Library, Recent, 56, 112, 168, 278, 333, 389, 502, 557, 625, 686
Address of the retiring President, Arthur F. Chace, 123
Air-Borne infection, the rationale and means of disinfection of air, 393
Alcoholism, Physician and the problem of, Howard W. Haggard, 451
Alloxan diabetes, its production and mechanism, Martin G. Goldner, 44
Anderson, Donald G., Clinical observations on the treatment of various infections with penicillin, 581
Annan, Gertrude L., Medical libraries and medical history, 163
Annual meeting of the Academy, January 4, 1945
  Address of the retiring President, Arthur F. Chace, 123
  Diverse clinical picture of coronary heart disease, Robert L. Levy, 171
  Scientific humanism in this changing world, Presidential address, W. W. Herrick, 115
  Treatment of coronary disease, Charles C. Wolferth, 185
Arthritis, Penicillin and sulfonamides in the treatment of osteomyelitis and pyogenic, J. Albert Key, 87

Benjamin, J. A., W. W. Scott and, Role of bilateral orchiectomy in the treatment of carcinoma of the prostate gland, 307
Biggs (Hermann M.) Memorial Lecture, Medical and public health importance of the insecticide DDT, Fred C. Bishopp, 561
Binger, Carl, Critique of psychotherapy in arterial hypertension, 610
Biological factors in human disease, Certain, George Draper, 599
Bishopp, Fred C., Medical and public health importance of the insecticide DDT, 561
Bubble formation in blood and tissues, Decompression sickness and, E. Newton Harvey, 505
Cardiac enlargement; its recognition and significance, Harry E. Ungerleider, 482
Carpenter (Wesley M.) Lecture, Influenza, methods of study and control, Thomas Francis, Jr., 337
Casals, J., Peter K. Olitsky and, Concepts of the immunology of certain virus infections, 356
Cecil, Russell L., Chemotherapy in acute upper respiratory infections, 263
Certain biological factors in human disease, George Draper, 599
Chace, Arthur F., Address of the retiring President, 123
Chemoprophylaxis of streptococcus disease, Hugh J. Morgan and Roy H. Turner, 37
Chemotherapeutic agents, Mode of action of, Rene J. Dubos, 27
Chemotherapy in acute upper respiratory infections, Russell L. Cecil, 263
  of gonorrhea, J. F. Mahoney and C. J. Van Slyke, 18
  of syphilis, Joseph Earle Moore, 3
Clinical observations on the treatment of various infections with penicillin, Donald G. Anderson, 581
Clinical Research Meeting (Abstracts)
  Clinical response in general paresis to treatment with penicillin, Edwin J. Doty, Herbert Koteen and Walsh McDermott, 434
  Comparison of several special preparations of protamine zinc insulin in the treatment of diabetes mellitus, Henry Dolger, 436
  Effect of bed rest and immobilization upon physiological and chemical functions in normal men, John Deitrick and Donald Whedon, 437
  Electrocardiographic changes during intravenous therapy of pneumonia, David D. Rutstein, K. Jefferson Thomson and Daniel K. Tolmach, 433
  Experimental study on the activity of penicillin administered orally in experimental streptococcus, pneumococcus and meningococcus infection of mice, R. J. Schnitzer, N. Ercoli, D. J.

Longacre and G. Soo-Hoo, 447
Functional pathology of experimental frostbite and the prevention of subsequent gangrene, Kurt Lange and Linn J. Boyd, 441
Improved technique for preparing a buried dermal graft in hernial repair, James V. Scola, 439
Heparin in the treatment of experimental human frost bite, Leo Loewe, Kurt Lange and Philip Rosenblatt, 442
Investigation of type specific meningococcic agglutinins in human serum: II—Immunologic response of proved cases of meningococci infection, Carolyn R. Falk and Emanuel Appelbaum, 445
Methods for achieving optimum penicillin blood levels including the use of enhancing agents such as para-aminohippuric acid, Leo Loewe, Philip Rosenblatt and Erna Alture-Werber, 444
Modified insulin technique in the treatment of ambulant psychiatric patients, Richard M. Brickner, 435
Morphological studies of Salmonella typhi murium and Salmonella enteridis in guinea pigs and mice, Alfred Angrist and Mollie Mollov, 446
Objective and clinical study of the normal, desquamated and atrophic tongues, Joseph R. DiPalma, 434
Oral administration of penicillin for treatment of gonococcal infections, Alfred Cohn, Borris A. Kornbluth and Isaak Grunstein, 446
Oral administration of penicillin in normal subjects and in patients with pneumococcus pneumonia, Walsh McDermott, Paul A. Bunn, Maria Benoit, Rebeckah Du Bois and Willetta Haynes, 443
Personality reaction to crime and disease, David Abrahamson, 435
Proteolytic activity of serum and plasma, L. R. Christensen and Colin M. Macleod, 447
Pulmonary suck and blow as a respiratory analeptic, interdependence of cardiac massage and suck-and-blow resuscitation, Jacob Reicher, 440
Rationale of sodium salts in the treatment of shock, Charles L. Fox, Jr., 438
Reaction of the peripheral circulation to cold in scleroderma, Raynaud's disease and thrombo-angiitis obliterans, H. R. Miller, J. Marrus and Beverly C. Smith, 441
Repository injection of penicillin in water-in-oil emulsion, effect on gonorrhea, A. Cohn, B. A. Kornbluth, J. Grunstein, K. J. Thomson and Jules Freund, 442
Significance of nutritional deficiency in diabetes, Morton S. Biskind and Herbert Schreier, 436
Streptomycin in the treatment of typhoid fever, Hobart A. Reimann, Alison H. Price and William F. Elias, 433
Subclinical trichinosis, a clinical and pathologic study, S. E. Gould, 444
Sudden deaths in infancy, Jacob Werne and Irene Garrow, 445
Therapeutic effect of radioactive iodine on adenocarcinoma of the thyroid with functioning metastases, S. M. Seidlin and L. D. Marinelli, 440
Use of radioactive sodium in studies of circulation in the extremities, Beverly C. Smith and Edith H. Quimby, 448
Coburn, Alvin C., Mass sulfadiazine prophylaxis of respiratory diseases in the U. S. Navy, 281
Combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, Leo Loewe, 59
Commission on Acute Respiratory Diseases, John H. Dingle, Director, Present status of the etiology of primary atypical pneumonia, 235
Concepts of the immunology of certain virus infections, Peter K. Olitsky and J. Casals, 356
Coronary disease, Treatment of, Charles C. Wolferth, 185
heart disease, Diverse clinical picture of, Robert L. Levy, 171
Co Tui, Value of protein and its chemical components (amino acids) in surgical repair, 631
Critique of psychotherapy in arterial hypertension, Carl Binger, 610

DDT, Medical and public health importance of the insecticide, Fred C. Bishopp, 561
Deaths, 56, 390, 689
Agatston, Sigmund Arthur, 689

Albee, Fred Houdlett, 390
Alger, Ellice Murdoch, 390
Baker, Sara Josephine, 390
Boylan, James Philip, 689
Brown, Aaron, 390
Bugbee, Henry Greenwood, 390
Busby, Archibald H., 689
Byrne, Joseph, 689
Cannon, Walter Bradford, 689
Carrel, Alexis, 56
Conaway, Walt P., 689
Currier, Charles Gilman, 390
Darlington Thomas, 689
Dawson, Martin H., 689
Ditman, Norman Edward, 390
Dixon, George Sloan, 56
Eckerson, Edwin B., 689
Faulkner, James Francis, 390
Fischer, Louis, 689
Foote, Edward Milton, 390
Friesner, Isadore, 689
Gibson, Charles Langdon, 56
Goodman, Charles, 689
Grauer, Frank, 390
Harrop, George A., 689
Herrick, William Worthington, 689
Howell, William Henry, 390
Huhr, Lee Maidment, 689
Irving, Peter, 390
Jelliffe, Smith Ely, 689
Kerley, Charles G., 689
Koplik, Lewis Henry, 689
Levin, Isaac, 689
Lewis, Sir Thomas, 689
Linder, William, 690
McKeown, Hugh Spencer, 56
McSweeny, Edward Sherman, 56
Malcolm, Percy E. D., 690
Martin, Thomas A., 690
Meeker, Harold Denman, 690
Morris, Robert Tuttle, 390
Offenbach, Robert, 690
Rolleston, Sir Humphrey, 56
Schoenberg, Mark Joseph, 390
Schwarz, Herman, 690
Silver, Henry Mann, 690
Smith, Dorland, 690
Tilton, Benjamin Trowbridge, 690
Toms, S. W. Spencer, 690
Truesdell, Edward D., 690
Vineberg, Hiram, 690
Warsaw, Meyer Claudius, 390
Weissberg, Morris, 690
Wilson, Margaret Barclay, 690
Young, Anna Rand, 390

Decompression sickness and bubble formation in blood and tissues, E. Newton Harvey, 505
Diabetes, Alloxan, its production and management, Martin J. Goldner, 44
Differences in the nature of antibacterial action of the sulfonamides and penicillin and their relation to therapy, Colin M. MacLeod and Edna R. Stone, 375
Dingle, John H., Director, Commission on Acute Respiratory Diseases, Present status of the etiology of primary atypical pneumonia, 235
Disease, Certain biological factors in human, George Draper, 599
Reactions of tissues following infection and their place in an environmental conception of the nature of, Wiley D. Forbus, 127
Distant secondary circulatory and vasomotor reactions to accidental electric shock, George H. Hyslop, 302
Diverse clinical picture of coronary heart disease, Robert L. Levy, 171
Draper, George, Certain biological factors in human disease, 599
Dubos, Rene J., Mode of action of chemotherapeutic agents, 27

Earle, David P., Jr., James A. Shannon and, Recent advances in the treatment of malaria, 467
Electric shock, Distant secondary circulatory and vasomotor reactions to accidental, George H. Hyslop, 302
Endocarditis, Combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, Leo Loewe, 59
Experiences with rheumatic fever in the Army, Irving S. Wright, 419

Factors determining the dosage of penicillin in the treatment of infections, Charles H. Rammelkamp and William M. M. Kirby, 656
Ferguson, L. Kraeer, Treatment of burns and war wounds, 127
Forbus, Wiley D., Reactions of tissues following infection and their place in an environmental conception of the nature of disease, 145
Francis, Thomas, Jr., Influenza, methods of study and control, 337

Friday Afternoon Lectures
Physician and the problem of alcoholism, Howard W. Haggard, 451
Recent advances in the treatment of malaria, James A. Shannon and David P. Earle, Jr., 467
Shock therapy of psychoses, evidence for and against damage, Nolan D. C. Lewis, 673

γ-Globulin in the prevention and attenuation of measles, Use of concentrated human serum, Charles A. Janeway, 202
Goldner, Martin G., Alloxan diabetes, its production and management, 44
Gomori, George, Histology of the normal and diseased pancreas, 99
Gonorrhea, chemotherapy of, J. F. Mahoney and C. J. Van Slyke, 18
Gould, S. E., Trichinosis, a major health problem in the United States, what shall be done about it? 616
Graduate Fortnight, 1944
Chemoprophylaxis of streptococcus disease, Hugh J. Morgan and Roy H. Turner, 37
Chemotherapy in acute upper respiratory infections, Russell L. Cecil, 263
Chemotherapy of gonorrhea, J. F. Mahoney and C. J. Van Slyke, 18
Chemotherapy of syphilis, Joseph Earle Moore, 3
Combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, Leo Loewe, 59
Differences in the nature of antibacterial action of the sulfonamides and penicillin and their relation to therapy, Colin M. MacLeod and Edna R. Stone, 375
Influenza, methods of study and control, Thomas Francis, Jr., 337
Mass sulfadiazine prophylaxis of respiratory diseases in the U. S. Navy, Alvin F. Coburn, 281
Mode of action of chemotherapeutic agents, Rene J. Dubos, 27
Penicillin and sulfonamides in the treatment of osteomyelitis and pyogenic arthritis, J. Albert Key, 87
Present status of the etiology of primary atypical pneumonia, Commission on Acute Respiratory Diseases, John H. Dingle, Director, 235
Reactions of tissues following infection and their place in an environmental conception of the nature of disease, Wiley D. Forbus, 145
Treatment of burns and war wounds, L. Kraeer Ferguson, 127
Use of concentrated human serum γ-globulin in the prevention and attenuation of measles, Charles A. Janeway, 202

Haggard, Howard W., Physician and the problem of alcoholism, 451
Harvey Lecture, Decompression sickness and bubble formation in blood and tissues, E. Newton Harvey, 505
Harvey, E. Newton, Decompression sickness and bubble formation in blood and tissues, 505
Heart disease, Diverse clinical picture of coronary, Robert L. Levy, 171
Herrick, William Worthington, Obituary, Josephine Hemingway Kenyon, 499
Scientific humanism in this changing world, Presidential address, 115
Histology of the normal and diseased pancreas, George Gomori, 99
Hoagland, Charles L., Therapy of liver diseases, 537
Humanism in this changing world, Scientific, Presidential address, W. W. Herrick, 115
Hypertension, Critique of psychotherapy in arterial, Carl Binger, 610
Hyslop, George H., Distant secondary circulatory and vasomotor reactions to accidental electric shock, 302

In Memoriam. See Obituary
Infection, Reactions of tissues following, and their place in an environmental conception of the nature of disease, Wiley D. Forbus, 145
Influenza, methods of study and control, Thomas Francis, Jr., 337

Janeway, Charles A., Use of concentrated human serum γ-globulin in the prevention and attenuation of measles, 202

Kast (Ludwig) Lecture, Mode of action of chemotherapeutic agents, Rene J. Dubos, 27
Kenyon, Josephine Hemingway, William Worthington Herrick, Obituary, 499

Key, J. Albert, Penicillin and sulfonamides in the treatment of osteomyelitis and pyogenic arthritis, 87
Kirby, William M. M., Charles H. Rammelkamp and, Factors determining the dosage of penicillin in the treatment of infections, 656
Klingman, Walter O., Some psychiatric aspects of nervous system injuries, 225

Levy, Robert L., Diverse clinical picture of coronary heart disease, 171
Lewis, Nolan D. C., Shock therapy of psychoses, evidence for and aaginst damage, 673
Library notes
Medical libraries and medical history, Gertrude L. Annan, 163
Recent accessions, 56, 112, 168, 278, 333, 389, 502, 557, 625, 686
Liver diseases, Therapy of, Charles L. Hoagland, 537
Loewe, Leo, Combined use of anti-infectives and anticoagulants in the treatment of subacute bacterial endocarditis, 59

MacLeod, Colin M. and Edna R. Stone, Differences in the nature of antibacterial action of the sulfonamides and penicillin and their relation to therapy, 375
Mahoney, J. F. and C. J. Van Slyke, Chemotherapy of gonorrhea, 18
Malaria, Recent advances in the treatment of, James A. Shannon and David P. Earle, Jr., 467
Mass sulfadiazine prophylaxis of respiratory diseases in the U. S. Navy, Alvin F. Coburn, 281
Measles, Use of concentrated human serum γ-globulin in the prevention and attenuation of, Charles A. Janeway, 202
Medical and public health importance of the insecticide DDT, Fred C. Bishopp, 561
libraries and medical history, Gertrude L. Annan, 163
Mode of action of chemotherapeutic agents, Rene J. Dubos, 27
More, Joseph Earle, Chemotherapy of syphilis, 3
Morgan, Hugh J. and Roy S. Turner, Chemoprophylaxis of streptococcus disease, 37
Mudd, Stuart, Air-borne infection, the rationale and means of disinfection of air, 393

Nervous system injuries, Some psychiatric aspects of, Walter O. Klingman, 225

Obituary, William Worthington Herrick, Josephine Hemingway Kenyon, 499
Olitsky, Peter K. and J. Casals, Concepts of the immunology of certain virus infections, 356
Orchiectomy in the treatment of carcinoma of the prostate gland, Role of bilateral, W. W. Scott and J. A. Benjamin, 307
Osteomyelitis and pyogenic arthritis, Penicillin and sulfonamides in the treatment of, J. Albert Key, 87

Pancreas, Histology of the normal and diseased, George Gomori, 99
Penicillin, Clinical observations on the treatment of various infections with, Donald G. Anderson, 581
in the treatment of infections, Factors determining the dosage of, Charles H. Rammelkamp and William M. M. Kirby, 656
and sulfonamides in the treatment of osteomyelitis and pyogenic arthritis, J. Albert Key, 87
and their relation to therapy, Differences in the nature of antibacterial action of the sulfonamides and, Colin M. MacLeod and Edna R. Stone, 375
Physician and the problem of alcoholism, Howard W. Haggard, 451
Pneumonia, Present status of the etiology of primary atypical, Commission on Acute Respiratory Diseases, John H. Dingle, Director, 235
Present status of the etiology of primary atypical pneumonia, Commission on Acute Respiratory Diseases, John H. Dingle, Director, 235
Presidential address, Scientific humanism in this changing world, W. W. Herrick, 115
Prostate gland, Role of bilateral orchiectomy in the treatment of carcinoma of the, W. W. Scott and J. A. Benjamin, 307
Protein and its chemical components (amino acids) in surgical repair, Value of, Co Tui, 631
Psychiatric aspects of nervous system injuries, Some, Walter O. Klingman, 225

Psychoses, Shock therapy of, evidence for and against damage, Nolan D. C. Lewis, 673
Psychotherapy in arterial hypertension, Critique of, Carl Binger, 610
Public health importance of the insecticide DDT, Medical and, Fred C. Bishopp, 561

Rammelkamp, Charles H. and William M. M. Kirby, Factors determining the dosage of penicillin in the treatment of infections, 656
Reactions of tissues following infection and their place in an environmental conception of the nature of disease, Wiley D. Forbus, 145
Recent accessions to the Library, 56, 112, 168, 278, 333, 389, 502, 557, 625, 686
advances in the treatment of malaria, James A. Shannon and David P. Earle, Jr., 467
Respiratory diseases in the U. S. Navy, Mass sulfadiazine prophylaxis of, Alvin F. Coburn, 281
infections, Chemotherapy in acute upper, Russell L. Cecil, 263
Rheumatic fever in the Army, Experiences with, Irving S. Wright, 419
Role of bilateral orchiectomy in the treatment of carcinoma of the prostate gland, W. W. Scott and J. A. Benjamin, 307

Scientific humanism in this changing world, Presidential address, W. W. Herrick, 115
Scott, W. W. and J. A. Benjamin, Role of bilateral orchiectomy in the treatment of carcinoma of the prostate gland, 307
Shannon, James A. and David P. Earle, Jr., Recent advances in the treatment of malaria, 467
Shock therapy of psychoses, evidence for and against damage, Nolan D. C. Lewis, 673
Some psychiatric aspects of nervous system injuries, Walter O. Klingman, 225
Stone, Edna R., Colin M. MacLeod and, Differences in the nature of antibacterial action of the sulfonamides and penicillin and their relation to therapy, 375
Streptococcus disease, chemoprophylaxis of, Hugh J. Morgan and Roy H. Turner, 37
Suiter (A. Walter) Lecture, Air-borne infection, The rationale and means of disinfection of air, Stuart Mudd, 393
Sulfadiazine prophylaxis, Mass, of respiratory diseases in the U. S. Navy, Alvin F. Coburn, 281
Sulfonamides and penicillin and their relation to therapy, Differences in the nature of bacterial action of the, Colin M. MacLeod and Edna R. Stone, 375
in the treatment of osteomyelitis and pyogenic arthritis, Penicillin and, J. Albert Key, 87
Syphilis, Chemotherapy of, Joseph Earle Moore, 3

Therapy of liver diseases, Charles A. Hoagland, 537
Treatment of burns and war wounds, L. Kraeer Ferguson, 127
of coronary disease, Charles C. Wolferth, 185
Trichinosis, a major health problem in the United States, what shall be done about it? S. E. Gould, 616
Turner, Roy H., Hugh J. Morgan and, Chemoprophylaxis of streptococcus disease, 37

Ungerleider, Harry E., Cardiac enlargement, its recognition and significance, 482
Use of concentrated human serum γ-globulin in the prevention and attenuation of measles, Charles A. Janeway, 202
Value of protein and its chemical components (amino acids) in surgical repair, Co Tui, 631
Van Slyke, C. J., J. F. Mahoney and, Chemotherapy of gonorrhea, 18
Vasomotor reactions to accidental electric shock, Distant secondary circulatory and, George H. Hyslop, 302
Virus infections, Concepts of the immunology of certain, Peter K. Olitsky and J. Casals, 356

War wounds, Treatment of burns and, L. Kraeer Ferguson, 127
Wolferth, Charles C., Treatment of coronary disease, 185
Wounds, Treatment of burns and war, L. Kraeer Ferguson, 127

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